A Randomized, Double-Blind, Placebo-Controlled, Phase 2a Study to Assess the Clinical Efficacy of ISIS 721744, a Second-Generation Ligand-Conjugated Antisense Inhibitor of Prekallikrein, in Patients With Hereditary Angioedema.

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IONIS PHARMACEUTICALS, INC.

ISIS 721744-CS2

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Original Protocol – 3 May 2019

EudraCT No: 2019-001044-22

Sponsor:

Ionis Pharmaceuticals, Inc.
2855 Gazelle Court
Carlsbad, CA 92010

ISIS 721744

Original Protocol

EudraCT No: 2019-001044-22

Clinical Phase: 2a

A Randomized, Double-Blind, Placebo-Controlled, Phase 2a Study to Assess the Clinical Efficacy of ISIS 721744, a Second-Generation Ligand-Conjugated Antisense Inhibitor of Prekallikrein, in Patients with Hereditary Angioedema

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Date: 3 May 2019

Confidentiality Statement

Protocol Signature Page

Protocol Number:	ISIS 721744-CS2
Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled, Phase 2a Study to Assess the Clinical Efficacy of ISIS 721744, a Second-Generation Ligand-Conjugated Antisense Inhibitor of Prekallikrein, in Patients with Hereditary Angioedema
Amendment:	Original Protocol
Date:	3 May 2019

I hereby acknowledge that I have read and understand the attached clinical protocol, entitled "A Randomized, Double-Blind, Placebo-Controlled, Phase 2a Study to Assess the Clinical Efficacy of ISIS 721744, a Second-Generation Ligand-Conjugated Antisense Inhibitor of Prekallikrein, in Patients with Hereditary Angioedema," dated 3 May 2019, and agree to conduct the study as described herein.

I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Ionis Pharmaceuticals, Inc.

Investigator's Signature

Investigator's Name *(please print)* Date (DD Month YYYY)

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PROTOCOL SYNOPSIS

Protocol Title	A Randomized, Double-Blind, Placebo-Controlled, Phase 2a Study to Assess the Clinical Efficacy of ISIS 721744, a Second-Generation Ligand-Conjugated Antisense Inhibitor of Prekallikrein, in Patients with Hereditary Angioedema
Study Phase	2a
Indication	Hereditary angioedema (HAE)
Primary Objective	The primary objective of the study is to evaluate the clinical efficacy of antisense inhibitor of prekallikrein (ISIS 721744) in patients with HAE type 1 (HAE-1), HAE type 2 (HAE-2), or HAE with normal C1-inhibitor (C1-INH).
Secondary Objectives	The secondary objectives of the study are to evaluate safety and tolerability of ISIS 721744 in patients with HAE-1/HAE-2 or HAE with normal C1-INH (HAE-nC1-INH) and to evaluate the effect of ISIS 721744 on plasma prekallikrein (PKK) and other relevant biomarkers.
Exploratory Objectives	The exploratory objectives of the study are to evaluate pharmacokinetics (PK) of ISIS 721744 (as a total full-length antisense oligonucleotide (ASO), including fully conjugated, partially conjugated, and unconjugated ISIS 721744) over time and to assess potential PK/pharmacodynamic (PD) correlations on relevant biomarkers and clinical outcomes, as appropriate.
Study Design	The study will be randomized, double-blind, and placebo-controlled in Part A and will be open-label in Part B.
Number of Patients	Approximately 24 patients with HAE are planned to be enrolled in the study: approximately 18 patients with HAE-1/HAE-2 are planned to be enrolled in Part A of the study, and, in parallel, approximately 6 patients with HAE-nC1-INH are planned to be enrolled in Part B of the study. Due to the rarity of HAE-nC1-INH, enrollment in Part B may be ended early if Study Centers are unable to enroll sufficient patients with HAE-nC1-INH; this will not impact completion of Part A.

PROTOCOL SYNOPSIS CONTINUED

Study Population	**Inclusion Criteria** 1. Patients must provide written informed consent (signed and dated) and any authorizations required by local law and be able to comply with all study requirements for the duration of the study. 2. Patients must be aged ≥ 18 years at the time of informed consent. 3. Patients must have a documented diagnosis of HAE-1/HAE-2 (for inclusion in Part A) or HAE-nC1-INH (for inclusion in Part B) as defined below: a. Documented diagnosis of HAE-1/HAE-2 based upon ALL of the following: i. Documented clinical history consistent with HAE (subcutaneous [SC] or mucosal, non-pruritic swelling episodes without accompanying urticaria) (Maurer et al. 2018). ii. Diagnostic testing results that confirm HAE-1/HAE-2: C1-INH functional level < 40% normal level. Patients with a functional level of 40% to 50% of normal can be enrolled if their complement factor C4 (C4) level is below the lower limit of normal (LLN) or if a known pathogenic mutation in the *SERPING1* gene has been demonstrated. iii. At least 1 of the following: age at reported HAE onset ≤ 30 years; a family history consistent with HAE-1/HAE-2; or complement component 1q within the normal range. b. Documented diagnosis of HAE-nC1-INH based upon documented clinical history consistent with HAE (SC or mucosal, non-pruritic swelling episodes without accompanying urticaria) (Maurer et al. 2018) AND any 1 of the following: i. A clinical diagnosis of bradykinin (BK)-mediated angioedema as confirmed with threshold-stimulated kallikrein activity and Investigator-confirmed response to acute use of a BK targeted treatment (icatibant or ecallantide). ii. One (1) of the established mutations (c.1032C>A, Thr309Lys; c.1032C>G, Thr309Arg; c.971_1018+24del72*; or c.892_909dup) in the factor XII gene. iii. The established mutation in the plasminogen gene (c.9886A>G, p.Lys330Glu). iv. The established mutation in the angiopoietin-1 gene (c.807G>T, p.A119S). 4. Patients must experience a minimum of 2 HAE attacks (assessed by the Angioedema Activity Score [AAS] and confirmed by the Investigator) during the Screening Period. 5. Patients must have access to, and the ability to use, ≥ 1 acute medication(s) (e.g., plasma-derived or recombinant C1-INH concentrate or a BK2-receptor antagonist) to treat angioedema attacks.

PROTOCOL SYNOPSIS CONTINUED

Study Population Continued	**Inclusion Criteria Continued** 6. Female patients must be non-pregnant (and not planning a pregnancy during the study) and non-lactating, and be either: a. Surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, or bilateral oophorectomy). b. Post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years of age, 12 months of spontaneous amenorrhea without an alternative medical cause and follicle-stimulating hormone [FSH] levels in the post-menopausal range for the laboratory involved). c. Abstinent (only acceptable as true abstinence, i.e., when in line with the preferred and usual lifestyle of the patient; periodic abstinence [e.g., calendar, ovulation, symptothermal, or post-ovulation methods], declaration of abstinence for the duration of the study, or withdrawal are not acceptable methods of contraception). d. If engaged in sexual relations of childbearing potential, agree to use highly effective contraceptive methods (refer to Section 6.3.1) from the time of signing the informed consent form (ICF) until at least 13 weeks after the last dose of Study Drug (ISIS 721744 or placebo). 7. Male patients must be surgically sterile or, if engaged in sexual relations with a female of childbearing potential, the patient must agree to use an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the ICF until at least 13 weeks after the last dose of Study Drug (ISIS 721744 or placebo). **Exclusion Criteria** 1. Anticipated use of short-term prophylaxis for angioedema attacks for a pre-planned procedure during the Screening or Study Periods. 2. Concurrent diagnosis of any other type of recurrent angioedema, including acquired or idiopathic angioedema. 3. Anticipated change in the use of concurrent androgen prophylaxis used to treat angioedema attacks. 4. Any clinically-significant abnormalities in screening laboratory values that would render a patient unsuitable for inclusion in the study. The following values are exclusionary: a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.5 x upper limit of normal (ULN). b. Bilirubin > 1.5 x ULN unless due to Gilbert's syndrome. c. Platelet count < LLN. d. Estimated glomerular filtration rate (eGFR) < 60 mL/min (as determined by the Cockcroft-Gault Equation for creatinine clearance).

PROTOCOL SYNOPSIS CONTINUED

Study Population Continued	**Exclusion Criteria Continued** 5. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to dosing. 6. Known history of or positive test for human immunodeficiency virus (HIV), hepatitis C, or chronic hepatitis B. 7. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix that has been successfully treated. 8. Treatment with another investigational drug or biological agent within 1 month or 5 half-lives, whichever is longer, of Screening. 9. Exposure to any of the following medications: a. Angiotensin-converting enzyme (ACE) inhibitors or any estrogen-containing medications with systemic absorption (such as oral contraceptive or hormonal replacement therapy) within 4 weeks prior to Screening. b. Chronic prophylaxis with Lanadelumab within 6 months prior to Screening. c. Oligonucleotides (including small interfering RNA) within 4 months of Screening if single dose received, or within 12 months of Screening if multiple doses received. Any condition that, in the opinion of the Investigator, may compromise the patient's safety or compliance, preclude successful conduct of the study, or interfere with the interpretation of results.
Prohibited Concomitant Medications	The following medications/procedures will not be permitted during the study: • Chronic prophylaxis for angioedema attacks, except for a stable dose of androgens. Any use of Lanadelumab will not be permitted. **NOTE:** The use of acute medications (plasma-derived or recombinant C1-INH concentrate or BK2-receptor antagonist) to treat angioedema attacks is allowed as medically indicated. • ACE inhibitors or any estrogen-containing medications with systemic absorption (such as oral contraceptive or hormonal replacement therapy). • Any oligonucleotides (including small interfering RNA) other than ISIS 721744. • Plasmapheresis. • Any other investigational drug or device.

PROTOCOL SYNOPSIS CONTINUED

Treatment Groups	A total of approximately 24 patients in Parts A and B combined will be administered SC injections of ISIS 721744 80 mg or placebo every 4 weeks. Patients will be allocated into Part A or Part B according to type of HAE, (i.e., either HAE-1/HAE-2 in Part A or HAE-nC1-INH in Part B) as follows: • In Part A, approximately 18 patients with HAE-1/HAE-2 will be randomized to SC injections of ISIS 721744 80 mg or placebo in a 2:1 ratio (ISIS 721744:placebo). • In Part B, approximately 6 patients with HAE-nC1-INH will be administered open-label SC injections of ISIS 721744 80 mg. Due to the rarity of HAE-nC1-INH, enrollment in Part B may be ended early if Study Centers are unable to enroll sufficient patients; this will not impact the completion of Part A.
Study Drug Dosage and Administration	The Study Drug (ISIS 721744 or placebo) is contained in 2-mL stoppered glass vials. The Study Drug (ISIS 721744 or placebo) and its storage and preparation instructions will be provided by the Sponsor or designee. The Study Drug (ISIS 721744 or placebo) must be stored securely at 2 °C to 8 °C and be protected from light. During the Treatment Period, Study Drug (ISIS 721744 or placebo) will be administered as a single SC injection every 4 weeks during on-site study visits.
Rationale for Dose and Schedule Selection	The dose level of 80 mg every 28 days was selected based on the safety, tolerability, PK, and PD data from the ISIS 721744-CS1 study in healthy volunteers. The Phase 1 study evaluated doses of 20, 40, 60, and 80 mg ISIS 721744 administered once every 4 weeks for a total of 12 weeks. All dose levels were generally well-tolerated and induced a dose- and exposure-dependent reduction in plasma PKK, a biomarker for BK and vascular permeability. The highest dose level of 80 mg produced near-complete reduction of plasma PKK levels (a mean reduction of 93.6% from Baseline on Day 99 [2 weeks after the last dose]). The estimated half-life ($t_{½}$) from the Phase 1 PK data was approximately 4 to 5 weeks, supporting the once-every-28-day dosing regimen. Pharmacokinetic/PD analysis of the Phase 1 data suggested very minor differences in plasma PKK reductions at doses higher than 80 mg.

PROTOCOL SYNOPSIS CONTINUED

Adjustment of Dose and/or Treatment Schedule	Down-titration of Study Drug (ISIS 721744 or placebo) will not be allowed during the study. Action taken with Study Drug (ISIS 721744 or placebo) due to an adverse event (AE) is characterized by 1 of the following: • None: No changes made to Study Drug (ISIS 721744 or placebo) administration and dose. • Not Applicable: AE reported during the Screening Period prior to Study Drug (ISIS 721744 or placebo) administration. • Permanently Discontinued: Study Drug (ISIS 721744 or placebo) discontinued and not restarted. • Temporarily Interrupted, Restarted – Same Dose: Dosing and/or dosing frequency temporarily interrupted/changed or delayed due to the AE and restarted at the same dose.
Study Visit Schedule and Procedures	The study will be conducted concurrently in 2 parts (Part A and Part B); patients will be allocated into Part A or Part B according to type of HAE (i.e., either HAE-1/HAE-2 in Part A or HAE-nC1-INH in Part B). Part A is randomized, double-blind, and placebo-controlled; and Part B is open-label. The study visit schedule and procedures are nearly identical in Part A and Part B, and thus are presented together; any differences are indicated where applicable. Patients will be screened for eligibility criteria following written informed consent. During the Screening Period, the following assessments will be performed: demographics; medical history, including a detailed HAE history; prior and concomitant medications, including type of prophylaxis (if used) and type of acute treatment; HIV, hepatitis B, and hepatitis C screening; pregnancy testing for women of childbearing potential and FSH testing for post-menopausal women; quality of life as assessed by the angioedema quality of life (AE-QoL) questionnaire; attack frequency, as assessed by the AAS daily during up to 8 consecutive weeks, and confirmed by the Investigator; HAE attack assessment; physical examinations, including vital signs, body height, and weight; electrocardiograms (ECGs); AEs; PD blood sampling; inflammatory panel; and clinical laboratory assessments (chemistry, hematology, coagulation, and urinalysis). Threshold-stimulated kallikrein activity will be assessed only in patients who have HAE-nC1-INH without a factor XII mutation or the plasminogen or angiopoietin-1 mutation. Genetic testing will be performed only for patients who do not have HAE genetic diagnostic testing results prior to Screening.

PROTOCOL SYNOPSIS CONTINUED

Study Visit Schedule and Procedures Continued	During the Screening Period, patients must experience a minimum of 2 HAE attacks (assessed by the AAS and confirmed by the Investigator) to be eligible for the study; patients will be instructed to report details of any HAE attack to the study site within 72 hours of the onset of the attack. Throughout the Screening Period, site personnel will contact the patient once a week (at approximately 7 days after the last contact with the patient) in order to solicit for any attack that may have occurred. If a patient experiences a third attack, the patient should be randomized as soon as possible, assuming all other screening activities have been completed and the patient meets all other eligibility requirements; in such cases, the Screening Period may be shorter than 8 weeks. During the course of the study, the use of acute medications (plasma-derived or recombinant C1-INH concentrate, BK2-receptor antagonist, or kallikrein inhibitor) to treat angioedema attacks is allowed as medically indicated. Patients can be treated with on-demand therapy as determined by their treating physician. After a Screening Period of up to 8 weeks, those patients who had at least 2 documented attacks (assessed by the AAS and confirmed by the Investigator) during the Screening Period will be enrolled and/or randomized to receive ISIS 721744 80 mg or placebo (Part A) or open-label ISIS 721744 80 mg (Part B) every 4 weeks for a total Treatment Period of 12 weeks. The first dose of Study Drug will be administered at the Study Center on Day 1. ISIS 721744 will be administered as a SC injection in the abdomen, thigh, or outer area of the upper arm. Study visits will be performed during the Treatment Period at Week 1 (Administration 1), Week 3 (safety monitoring), Week 5 (Administration 2), Week 9 (Administration 3), and Week 13 (Administration 4); and will be performed during the Post-Treatment Period at Weeks 17, 21, and 26. During the study, patients will be instructed to report details of any HAE attack to the study site within 72 hours of the onset of the attack. During the Treatment and Post-Treatment Periods, the following data will be collected: daily AAS and number of HAE attacks (assessed by the AAS and confirmed by the Investigator); number of HAE attacks that required on-demand treatment; HAE attack details, including localization, severity, course, and details of any required treatment (i.e., frequency and dose); and vital signs. Throughout the Treatment and Post-Treatment Periods, site personnel will contact the patient once a week (at approximately 7 days after the last contact with the patient) in order to solicit for any attack that may have occurred. In addition, during study visits, site personnel will solicit for any new HAE attack information that was not provided through patient contact with the site. See Section 6.2.1 for further information on the collection of data surrounding HAE attacks.

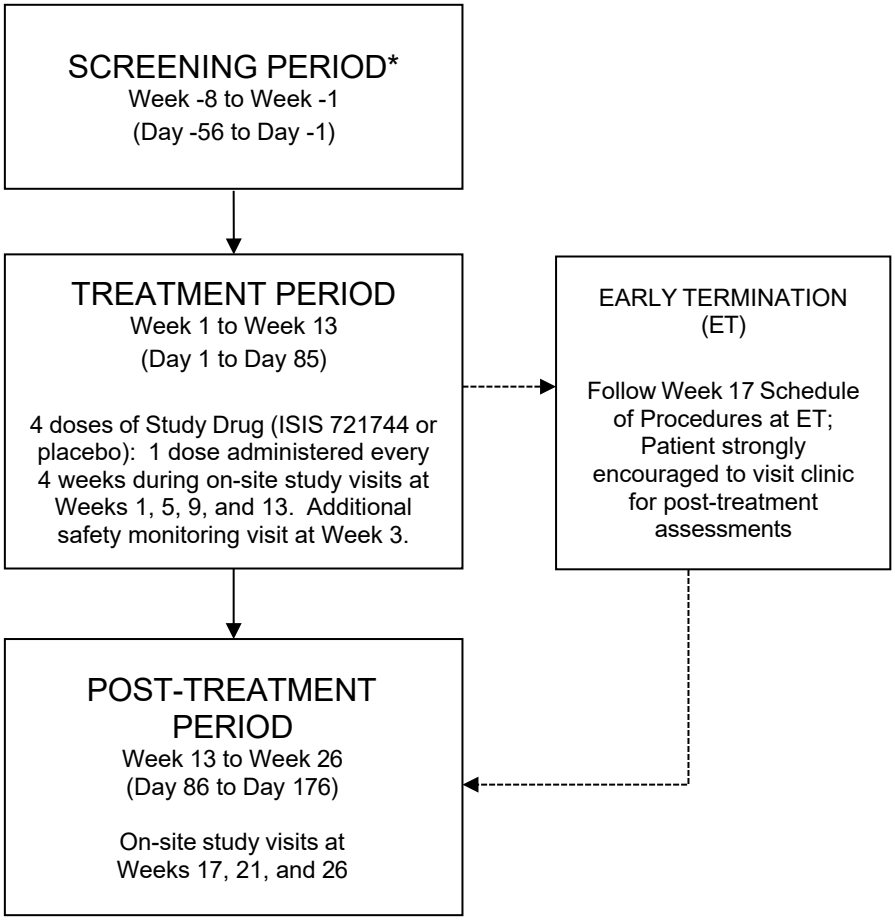
PROTOCOL SYNOPSIS CONTINUED

Study Visit Schedule and Procedures Continued	Additionally, blood will be collected at every visit during the Treatment and Post-Treatment Periods to assess PD and coagulation parameters, including, but not limited to: plasma PKK, plasma proenzyme activation, cleaved high molecular weight kininogen (cHK) levels, D-dimer levels, activated partial thromboplastin time (aPTT), plasmin-antiplasmin complexes, C4 split products, and platelet counts. Blood samples will also be collected regularly throughout the study for safety and PK/PD analyses. Additional assessments will be performed throughout the study as indicated in the Schedule of Procedures table in Appendix A. Patients who discontinue treatment will remain in the study and attend the Early Termination (ET) Visit unless consent is withdrawn. Detailed information regarding the study procedures is presented in Section 6 and Appendix A. Appendix B includes a list of laboratory analytes required for the study.
Primary Endpoint	The primary endpoint is the time-normalized number of HAE attacks (per month) from Week 1 to Week 17.
Secondary Endpoints	Secondary endpoints include the following: • The time-normalized number of HAE attacks (per month) from Week 5 to Week 17 • The time-normalized number of HAE attacks (per month) from Week 9 to Week 21 • The time-normalized number of moderate or severe HAE attacks (per month) from Week 5 to Week 17 • The time-normalized number of moderate or severe HAE attacks (per month) from Week 9 to Week 21 • The number of patients with a clinical response (defined as a ≥ 50%, ≥ 70%, or ≥ 90% reduction from Baseline in HAE attack rate) by Week 17 • The number of HAE attacks requiring acute therapy from Week 5 to Week 17 • cHK levels at Weeks 9 and 17 • PKK activity at Weeks 9 and 17 • Consumption of on-demand medication at Weeks 9 and 17 • AE-QoL questionnaire score at Weeks 9 and 17

PROTOCOL SYNOPSIS CONTINUED

Exploratory Endpoints	Exploratory endpoints include the following: • The number of HAE attack-free patients by Week 17 • PK parameters, including, but not limited to: maximum observed plasma concentration (C_{max}), time to C_{max}, area under the plasma concentration-time curve, and $t_{½}$ • Potential exposure-response analysis using relevant exposure parameters and biomarkers
Safety Endpoints	The safety and tolerability of ISIS 721744 will be assessed by determining the number, type, severity, and dose-relationship of AEs; vital signs; ECGs; and clinical laboratory parameters. Safety results in patients dosed with ISIS 721744 will be compared to safety results in patients dosed with placebo.
Statistical Considerations	The sample size of 18 patients with HAE-1/HAE-2 (12 patients administered SC injections of ISIS 721744 80 mg and 6 patients administered placebo) is from clinical considerations for sufficient safety and tolerability evaluation. The primary endpoint is the time-normalized number of HAE attacks (per month) from Week 1 to Week 17. From historical data, the placebo group is estimated to have 6.8 HAE attacks per 4-month period. If the ISIS 721744 80 mg group is assumed to have 2.8 HAE attacks per 4-month period, then with a 0.05 significance level and Poisson model, the sample size of 18 patients will provide at least 90% power for the primary endpoint, considering a 10% missing data or dropout rate for both active treatment and placebo. There is no statistical rationale for the sample size of 6 patients with HAE-nC1-INH. An independent Data and Safety Monitoring Board (DSMB) will be established prior to the initiation of the study. The DSMB will be responsible for monitoring the overall safe conduct of the study. Based on its ongoing assessment of the safety and tolerability of ISIS 721744, the DSMB will provide recommendations to the Sponsor for modifying, stopping, or continuing the study as planned. Details on the safety assessments, frequency of review, meeting schedules and controlled access to unblinded data are outlined in the DSMB Charter and Statistical Analysis Plan.
Sponsor	Ionis Pharmaceuticals, Inc.

STUDY DESIGN AND TREATMENT SCHEMA



*The Screening Period is up to 8 weeks in duration. A patient may be randomized after fewer than 8 weeks of Screening if the patient experiences > 2 HAE attacks in less than 8 weeks and has completed all other screening activities and has met all other eligibility requirements.

STUDY GLOSSARY

Abbreviation	Definition
2′-MOE	2′-*O*-(2-methoxyethyl)
AAS	Angioedema Activity Score
ACE	angiotensin-converting enzyme
ADR	adverse drug reaction
AE(s)	adverse event(s)
AE-QoL	angioedema quality of life
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
ASO	antisense oligonucleotide
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
Bb	complement factor Bb (activated complement split product)
βhCG	beta-subunit of human chorionic gonadotropin (pregnancy test)
BK	bradykinin
BUN	blood urea nitrogen
C	centigrade
C1-INH	C1-inhibitor
C4	complement factor C4
C5a	complement factor C5a (activated complement split product)
cHK	cleaved high molecular weight kininogen
C_{max}	maximum observed plasma concentration
CTCAE	Common Terminology Criteria for Adverse Events
dL	deciliter
DNA	deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic Case Report Form
eGFR	estimated glomerular filtration rate
ET	Early Termination
FSH	follicle-stimulating hormone
$GalNAc_3$	*N*-acetyl galactosamine
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HAE	hereditary angioedema
HAE-1	hereditary angioedema type 1
HAE-2	hereditary angioedema type 2
HAE-nC1-INH	hereditary angioedema with normal C1-inhibitor
HIV	human immunodeficiency virus
HK	high molecular weight kininogen
hs-CRP	C-reactive protein measured by high sensitivity assay
ICF	informed consent form

ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IgM	immunoglobulin M
INR	international normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISIS 721744	antisense inhibitor of prekallikrein
ITT	Intent-to-Treat
LCRIS	local cutaneous reaction at injection site
LLN	lower limit of normal
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA™	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid
NCS	not clinically-significant
PD	pharmacodynamic(s)
pH	measure of the acidity or basicity of a solution
PK	pharmacokinetic(s)
PKa	plasma kallikrein
PKK	prekallikrein
PP	Per-Protocol
PT	prothrombin time
RNA	ribonucleic acid
RNase H1	an ubiquitous endonuclease that specifically hydrolyzes the RNA strand in RNA/DNA hybrids
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous(ly)
Study Day 1	defined as the first day Study Drug is administered to the patient
Study Drug	ISIS 721744 or placebo
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	half-life
T3	triiodothyronine
T4	thyroxine
TEAE	treatment-emergent adverse event
t_{max}	time to maximum observed plasma concentration
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
WBC	white blood cell
WOCBP	woman/women of childbearing potential

1. OBJECTIVES AND ENDPOINTS

1.1. Objectives

1.1.1. Primary Objective

The primary objective of the study is to evaluate the clinical efficacy of antisense inhibitor of prekallikrein (ISIS 721744) in patients with hereditary angioedema (HAE) type 1 (HAE-1), HAE type 2 (HAE-2), or HAE with normal C1-inhibitor (C1-INH).

1.1.2. Secondary Objectives

The secondary objectives of the study are to evaluate safety and tolerability of ISIS 721744 in patients with HAE-1/HAE-2 or HAE with normal C1-INH (HAE-nC1-INH) and to evaluate the effect of ISIS 721744 on plasma prekallikrein (PKK) and other relevant biomarkers.

1.1.3. Exploratory Objectives

The exploratory objectives of the study are to evaluate pharmacokinetics (PK) of ISIS 721744 (as a total full-length antisense oligonucleotide [ASO], including fully conjugated, partially conjugated, and unconjugated ISIS 721744) over time and to assess potential PK/pharmacodynamic (PD) correlations on relevant biomarkers and clinical outcomes, as appropriate.

1.2. Study Endpoints

1.2.1. Primary Endpoints

The primary endpoint is the time-normalized number of HAE attacks (per month) from Week 1 to Week 17.

1.2.2. Secondary Endpoints

Secondary endpoints include the following:

- The time-normalized number of HAE attacks (per month) from Week 5 to Week 17
- The time-normalized number of HAE attacks (per month) from Week 9 to Week 21
- The time-normalized number of moderate or severe HAE attacks (per month) from Week 5 to Week 17
- The time-normalized number of moderate or severe HAE attacks (per month) from Week 9 to Week 21
- The number of patients with a clinical response (defined as a ≥ 50%, ≥ 70%, or ≥ 90% reduction from Baseline in HAE attack rate) by Week 17
- The number of HAE attacks requiring acute therapy from Week 5 to Week 17
- Cleaved high molecular weight kininogen (cHK) levels at Weeks 9 and 17
- PKK activity at Weeks 9 and 17

- Consumption of on-demand medication at Weeks 9 and 17
- Angioedema quality of life (AE-QoL) questionnaire score at Weeks 9 and 17

1.2.3. Safety Endpoints

The safety and tolerability of ISIS 721744 will be assessed by determining the number, type, severity, and dose-relationship of adverse events (AEs); vital signs; electrocardiograms (ECGs); and clinical laboratory parameters. Safety results in patients dosed with ISIS 721744 will be compared to safety results in patients dosed with placebo.

1.2.4. Exploratory Endpoints

Exploratory endpoints include the following:

- The number of HAE attack-free patients by Week 17
- PK parameters, including, but not limited to: maximum observed plasma concentration (C_{max}), time to C_{max} (t_{max}), area under the plasma concentration-time curve (AUC), and half-life ($t_{½}$)
- Potential exposure response analysis using relevant exposure parameters and biomarkers

2. BACKGROUND AND RATIONALE

2.1. Overview of Disease

Hereditary angioedema is a rare genetic disorder that is characterized by disabling recurrent episodes of local skin swellings, painful abdominal attacks, and, occasionally, laryngeal attacks that can be life-threatening. The disorder is classified in 3 subtypes. Hereditary angioedema type 1 and HAE-2 are caused by an autosomal dominant mutation in the *SERPING1* gene, resulting in either decreased levels of C1-INH (HAE-1) or loss-of-function of this protein (HAE-2) (Bissler et al. 1997). The third form of HAE is associated with normal levels and function of C1-INH (HAE-nC1-INH). This form is currently categorized as 4 subtypes, with either specific genetic mutations in the factor XII gene, the plasminogen gene, or the angiopoietin-1 gene, or due to an unknown cause (Maurer et al. 2018). Extensive evidence from *in vitro* and *in vivo* studies supports the key role of bradykinin (BK) in HAE attacks, although the data linking HAE-nC1-INH with BK are less strong (Zuraw and Christiansen 2016). Diagnosing HAE-nC1-INH can be challenging given the large heterogeneity of this patient population, the lack of diagnostic tests, and the fact that specific genetic mutations account only partially for the occurrence of this type of HAE. Recently, a threshold-stimulated kallikrein activity assay was shown to discriminate BK-mediated angioedema from histamine-mediated angioedema (Lara-Marquez et al. 2018). This technique may, therefore, enhance the identification of HAE-nC1-INH patients that are likely to benefit from inhibition of the contact activation pathway.

Treatment options for HAE include on-demand treatment of attacks and prophylaxis. On-demand options include supplementation of C1-INH (either plasma-derived or recombinant

C1-INH concentrate) and inhibition of BK2 receptor activation (BK2-receptor antagonist). In addition, tranexamic acid may relieve symptoms in non-severe angioedema attacks. Prophylactic regimens for HAE include plasma-derived C1-INH concentrate (administered either intravenously or subcutaneously [SC]), attenuated androgens, antifibrinolytics and a recently Food and Drug Administration-approved monoclonal antibody directed against plasma kallikrein (PKa). Kallikrein circulates in plasma as a zymogen (i.e., PKK) which is bound to one of its main substrates, high molecular weight kininogen (HK). Prekallikrein is cleaved upon contact activation, forming the active protease PKa. Plasma kallikrein cleaves HK in turn, thereby releasing BK and the split product cHK. The binding of BK to the BK2 receptor leads to activation of various intracellular signaling pathways resulting in vasodilation, chemotaxis of neutrophils, and increased vascular permeability and fluid efflux, which typically characterize an angioedema attack (Zuraw and Christiansen 2016).

2.2. Therapeutic Rationale

ISIS 721744 is a second-generation, ligand-conjugated ASO drug designed to reduce the production of PKK. Antisense technology is characterized by its high specificity in inhibiting a single-gene product, thereby diminishing the potential for off-target drug effects. Furthermore, since the drug discovery and development of antisense drugs is less costly than traditional small-molecule drugs, the availability of a plasma PKK inhibitor could be of additional value to the arsenal of prophylactic drugs for the prevention of HAE attacks. The long $t_{½}$ of second-generation antisense drugs and the lower frequency of administration afforded by ligand conjugation might provide additional benefit to patients.

The Phase 1 clinical data show that ISIS 721744 inhibits plasma PKK effectively in a dose-dependent manner without safety concerns.

2.3. ISIS 721744

2.3.1. Mechanism of Action

ISIS 721744 is an *N*-acetyl galactosamine ($GalNAc_3$)-conjugated, second-generation ASO drug targeted to human PKK. It is complementary to the translated regions (Exon 9) of the PKK protein messenger ribonucleic acid (mRNA) and, following cleavage of the $GalNAc_3$ moiety, binds to the mRNA by Watson and Crick base pairing. The hybridization (binding) of ISIS 721744 to the cognate mRNA results in the ubiquitous endonuclease that specifically hydrolyzes the RNA strand in RNA/DNA hybrids (RNase H1)-mediated degradation of the PKK mRNA, thus preventing production of the PKK protein. Maximal antisense-mediated reduction of target mRNA levels is typically greater than 90% of control levels in sensitive tissues (Crooke and Bennett 1996; Zhang et al. 2010). Furthermore, reduction in target mRNA levels using this approach correlates directly with a subsequent reduction in target protein levels.

2.3.2. Chemistry

Chemically, ISIS 721744 is a synthetic oligomer of 20 nucleotides (i.e., a 20-mer) that are connected sequentially by phosphorothioate and phosphodiester linkages (mixed backbone design). The nucleotide sequence of ISIS 721744 (Figure 1) is complementary to a 20-nucleotide stretch within Exon 9 of the PKK protein mRNA. Structurally, the

oligonucleotide has 4 regions. Two (2) of them, the 5 nucleotides at the 5' end and the 5 nucleotides at the 3' end, are composed of 2'-O-(2-methoxyethyl) (2'-MOE)-modified ribonucleotides. These 2'-MOE-modified nucleotides confer (1) increased affinity to the target mRNA (Altmann et al. 1996; McKay et al. 1999), (2) increased resistance to exonucleases and endonucleases (thereby increasing stability in tissue) (Geaiy et al. 2003), and (3) amelioration of some of the high-dose toxicities thereby resulting in an improved safety profile compai·ed to first-generation antisense chugs containing phosphorothioate modified oligodeoxynucleotides (Herny et al. 2000). The third region, the central po1tion of the oligonucleotide, is composed of 10 oligodeoxynucleotides. This chimeric design is called a MOE-Gapmer, and ISIS 721744 employs this chimeric structure to enable use of the RNase HI-mechanism for antisense activity. This is because while the 2'-MOE modification confers increased stability and affinity, it does not suppo1t RNase HI-catalyzed cleavage of ribonucleic acid (RNA) hybridized to 2'-MOE-modified nucleotides (McKay et al. 1999). This is caused by confo1mational changes induced in the heteroduplex by 2'-alkoxy:RNA hybrids that are not recognized by RNase HI enzyme (Inoue et al. 1987; Monia et al. 1993). By limiting the 2'-MOE modification to nucleotides flanking the phosphorothioate oligodeoxynucleotide core, the beneficial attributes of the 2'-MOE chemist1y ai·e preserved while also retaining RNase HI recognition. A fomth region, comprised of a u-iantenna1y cluster of GalNAc3 sugars, is linked to the 5' end of ISIS 721744 via a phosphodiester linkage. The GalNAc3 cluster is a high-affinity ligand for the asialoglycoprotein receptor, a receptor expressed primarily on the surface of liver hepatocytes (Stockert 1995). The GalNAc3 cluster enhances delive1y of ISIS 721744 to liver hepatocytes over other cell types and enhances potency. After internalization into cells, the GalNAc3 cluster is metabolized to release "free ASO" inside the cell (Prakash et al. 2014). The intemucleosidic linkages are a mixture of phosphorothioate and phosphodiester. The phosphorothioate linkages are introduced into the deoxyribonucleic acid (DNA) gap region and at both ends of the oligonucleotide to protect it from nuclease mediated metabolism. The mixed backbone design reduces the total number of phosphorothioate linkages, which reduces non-specific interactions with proteins and finther enhances potency and therapeutic index of GalNAc3-conjugated ASOs.

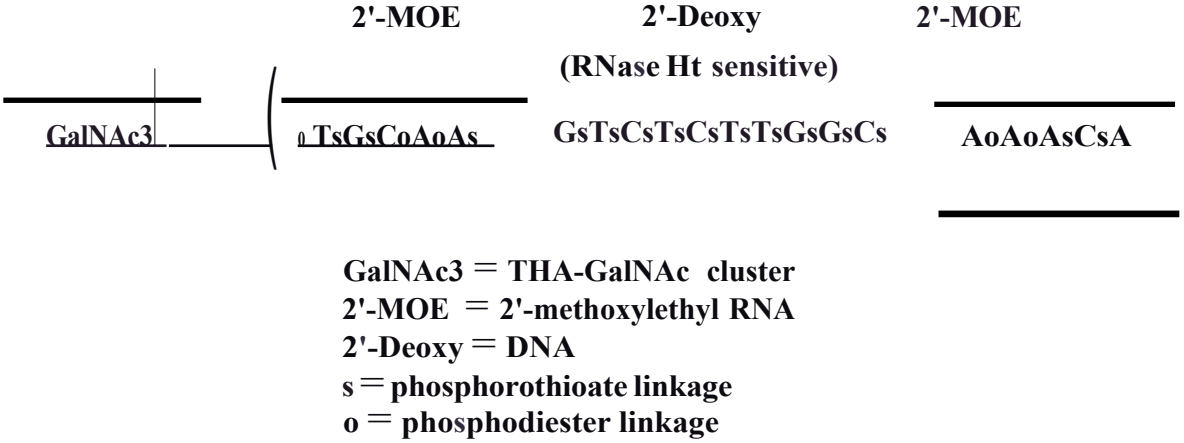


Figure 1: Design of GalNAc3-Conjugated Chimeric 2'-MOE Phosphorothioate Oligonucleotides (MOE-Gapmer)

The sequence ofISIS 721744 is shown.

2.3.3. Preclinical Experience

Detailed information concerning the preclinical studies conducted with PKK ASO ISIS 546254, its 5′-GalNAc$_3$-conjugated mixed backbone variant ISIS 721744, and mouse surrogate PKK ASOs can be found in the Investigator's Brochure.

The results support the concept that inhibition of PKK through antisense mechanism may serve as a new and effective strategy for the prophylaxis of HAE. Results also strongly support that GalNAc$_3$-conjugation of PKK ASO significantly increases the potency of ASO for inhibition of PKK hepatic mRNA and circulatory protein expression and thus these ASOs should be a useful therapeutic strategy for the prophylactic treatment of HAE.

2.3.4. Clinical Experience

ISIS 721744 has been evaluated in the clinical setting in a Phase 1 safety study (ISIS 721744-CS1). All subjects have completed study procedures and final safety and PD data are available. A summary is included below. Please refer to the Investigator's Brochure for a detailed description of the preclinical pharmacology, nonclinical toxicology and PK, as well as a description of previous clinical experience with other related 2′-MOE phosphorothioate oligonucleotides.

ISIS 721744 has been studied in 32 healthy volunteers in a double-blind, multiple-dose, dose-escalation study. Of these, 24 subjects received multiple doses of ISIS 721744. The 32 subjects were randomized into 4 cohorts (6 subjects each) to receive once-every-4-week SC doses of ISIS 721744 20, 40, 60, or 80 mg, or placebo (8 subjects) for a total of 12 weeks (4 total doses). All subjects received all planned doses of Study Drug (ISIS 721744 or placebo). The duration of Study Drug exposure was 84 days for each subject.

No serious adverse events (SAEs) were reported in the ISIS 721744-CS1 study. There were no early discontinuations from Study Drug or the study, and all subjects in the ISIS 721744 and placebo arms completed all study procedures. Adverse events at the injection site (defined as any preferred term containing "injection site") were the most commonly reported treatment-emergent adverse events (TEAEs) in the ISIS 721744 treatment arms; no injection site-related TEAEs were reported in the placebo arm. There were no flu-like reactions or events of local cutaneous reaction at injection site (LCRIS) reported; LCRIS events were defined as (A) moderate or severe injection site erythema, swelling, pruritus, pain, or tenderness that started on the day of injection and persisted for at least 2 days; or (B) any AE at the injection site, regardless of severity, that led to discontinuation of Study Drug, where AE at the injection site was the principal reason for discontinuation. No relationship between incidence of TEAEs and the dose administered was observed.

Thirteen (13) AEs related to study treatment were reported for 4 (16.7%) subjects in the ISIS 721744 arm, and for 1 subject (2 events; 12.5%) in the placebo arm. One (1) subject each in the ISIS 721744 and placebo arm reported AEs of ECG T wave inversion (preferred term) that were assessed as related. Nine (9) of the total 13 related events with ISIS 721744 concerned injection site-related events and were reported by 1 subject in the 80 mg arm. Additional related events were tinnitus (1 subject, 1 event in the 60 mg arm), headache (1 subject, 1 event in the 60 mg arm), and epistaxis (1 subject, 1 event in the 20 mg arm). All TEAEs related to study treatment were mild in severity, and none were serious.

ISIS 721744 resulted in a dose-dependent reduction of PKK concentration and plasma proenzyme activation. The difference in absolute and percent change from Baseline for ISIS 721744 vs. placebo was statistically significant for PKK concentration for 40, 60, and 80 mg ($p \leq 0.043$) starting at Day 15, the first evaluation, and for 20 mg starting at Day 29, and for plasma proenzyme activation for all doses ($p \leq 0.002$) starting at Day 15. The nadir was generally reached around Day 71, when the percent reduction with the 80 mg dose was -93.2% for PKK concentration and -99.6% for plasma proenzyme activation.

The difference in absolute and percent change from Baseline in cHK for ISIS 721744 vs. placebo was not statistically significant at any visit.

Clinical data from other $GalNAc_3$-conjugated 2′-MOE-gapmer oligonucleotides suggest that enhanced delivery of ISIS 721744 to hepatocytes vs. non-parenchymal cells will result in similar PD results as ISIS 546254 at $1/10^{th}$ to $1/30^{th}$ of the dose (Viney et al. 2016).

2.4. Rationale for Dose and Schedule of Administration

The dose level of 80 mg every 28 days was selected based on the safety, tolerability, PK, and PD data from the ISIS 721744-CS1 study in healthy volunteers. The Phase 1 study evaluated doses of 20, 40, 60, and 80 mg ISIS 721744 administered once every 4 weeks for a total of 12 weeks. All dose levels were generally well-tolerated and induced a dose- and exposure-dependent reduction in plasma PKK, a biomarker for BK and vascular permeability. The highest dose level of 80 mg produced near-complete reduction of plasma PKK levels (a mean reduction of 93.6% from Baseline on Day 99 [2 weeks after the last dose]). The estimated $t_{½}$ from the Phase 1 PK data was approximately 4 to 5 weeks, supporting the once-every-28-day dosing regimen. Pharmacokinetic/PD analysis of the Phase 1 data suggested very minor differences in plasma PKK reductions at doses higher than 80 mg.

2.5. Benefit-Risk Assessment

2.5.1. Benefit Assessment

The benefits of treatment of ISIS 721744 are currently unknown. Due to its mechanism of action, ISIS 721744 has the potential to be efficacious for the treatment of patients with HAE.

2.5.2. Risk Assessment

The known potential risks to study participants associated with ISIS 721744 are elaborated on in the “Guidance to Investigator” section of the Investigator’s Brochure.

There are no anticipated risks associated with reducing plasma PKK levels; however, a potential theoretical risk associated with PKK inhibition would be prolongation of activated partial thromboplastin time (aPTT). This risk is informed by 80 cases of PKK deficiency that have been described in the literature (Girolami et al. 2010). In these individuals, there is a discrepancy between an observed *in vitro* defect and an absence of bleeding. Thus, it is believed that most cases go undetected or, if detected, go unreported. Occasional bleeding or thrombosis has been reported in a few PKK deficient patients but these instances were due to the presence of associated risk factors. Diagnosis is based on the prolongation of partial thromboplastin time and normal prothrombin time (PT) and thrombin time. In these individuals, platelet and vascular

tests are normal and the long partial thromboplastin time has shown to be fully corrected by the addition of normal plasma or normal serum.

In monkeys, doses of ISIS 721744 of up to 30 mg/kg/wk for 13 weeks were well-tolerated with the exception of thrombocytopenia observed in 1 female at 12 mg/kg/wk and 1 male at 30 mg/kg/wk. The monkey dose of 6 mg/kg/wk provides an approximate 20-fold margin relative to a human dose of 80 mg every 4 weeks and therefore there is sufficient therapeutic margin to assure the safe clinical use of ISIS 721744 at the proposed clinical dose and regimen.

One (1) subject in the ISIS 721744-CS1 study had a confirmed platelet nadir count between 100 x 10^3/µL and the lower limit of normal (LLN) (140 x 10^3/µL). The subject received ISIS 721744 at 20 mg and had a platelet count of 139 x 10^3/µL on Study Day 99; all other reported values for this subject were within the reference range.

Platelet counts will be monitored closely throughout the clinical study.

More complete details can be found in the Investigator's Brochure.

2.5.3. Overall Assessment of Benefit:Risk

No specific risks have been identified with ISIS 721744. The AEs that occurred with the related drug ISIS 546254 were unrelated to reduction of PKK. In addition, the conjugated nature of ISIS 721744 is anticipated to reduce systemic exposure even further. Consequently, the platelet count reductions observed with the higher doses of the unconjugated molecule are not anticipated to occur at the dose tested in this study.

Taking into account the measures taken to minimize risk to patients participating in this study, the potential risks identified in association with ISIS 721744 are justified by the anticipated benefits that may be afforded to patients with HAE.

3. EXPERIMENTAL PLAN

3.1. Study Design

This Phase 2a study will be conducted at multiple Study Centers worldwide to assess the efficacy of ISIS 721744 in approximately 24 patients with HAE. Part A of the study will be randomized, double-blind, and placebo-controlled; Part B of the study will be open-label.

The study will be conducted concurrently in 2 parts (Part A and Part B); patients will be allocated into Part A or Part B according to type of HAE (i.e., either HAE-1/HAE-2 in Part A or HAE-nC1-INH in Part B). Part A is randomized, double-blind, and placebo-controlled; and Part B is open-label. The study visit schedule and procedures are nearly identical in Part A and Part B, and thus are presented together; any differences are indicated where applicable.

In Part A, approximately 18 patients with HAE-1/HAE-2 will be randomized to SC injections of ISIS 721744 80 mg or placebo in a 2:1 ratio (ISIS 721744:placebo). In Part B, approximately 6 patients with HAE-nC1-INH will be administered open-label SC injections of ISIS 721744 80 mg. Due to the rarity of HAE-nC1-INH, enrollment in Part B may be ended early if Study Centers are unable to enroll sufficient patients; this will not impact the completion of Part A.

Patients who discontinue treatment will remain in the study and attend the Early Termination (ET) Visit unless consent is withdrawn.

Detailed information regarding the study procedures is presented in Section 6 and Appendix A. Appendix B includes a list of laboratory analytes required for the study.

3.2. Number of Study Centers

This study will be conducted at multiple Study Centers worldwide.

3.3. Number of Patients

A total of approximately 24 patients in Parts A and B combined will be administered SC injections of ISIS 721744 80 mg or placebo every 4 weeks. Patients will be allocated into Part A or Part B according to type of HAE, (i.e., either HAE-1/HAE-2 or HAE-nC1-INH): approximately 18 patients with HAE-1/HAE-2 are planned to be enrolled in Part A of the study, and, in parallel, approximately 6 patients with HAE-nC1-INH are planned to be enrolled in Part B of the study. Due to the rarity of HAE-nC1-INH, enrollment in Part B may be ended early if Study Centers are unable to enroll sufficient patients with HAE-nC1-INH; this will not impact completion of Part A.

3.4. Overall Study Duration and Follow-up

The study will consist of Screening, Treatment, and Post-Treatment Periods. Please refer to the Schedule of Procedures in Appendix A.

Patients may be required to attend additional visits for monitoring of AEs or abnormal investigation results. The frequency of additional monitoring will be determined by the Sponsor Medical Monitor in consultation with the Investigator.

The length of each patient's participation in the study is approximately 8 months, which includes an up to 8-week Screening Period, a 12-week Treatment Period, and a 13-week Post-Treatment Period. Patients will receive fixed SC doses of Study Drug every 4 weeks during 4 on-site study visits as outlined in Appendix A.

3.4.1. Screening

Patient eligibility for the study will be determined within 8 weeks (56 days) prior to study entry.

3.4.2. Treatment Period

Eligible patients will report to the Study Center for the first administration of Study Drug on Study Day 1 (Week 1 Visit) and will continue to receive Study Drug once every 4 weeks during the 12-week Treatment Period. Patients will also return to the Study Center on Week 3 for a safety monitoring visit.

3.4.3. Post-Treatment Period

Patients are to return to the Study Center for post-treatment follow-up visits at Study Weeks 17, 21, and 26/ET. Patients may be required to attend additional visits for monitoring of AEs or

abnormal investigation results. The frequency of additional monitoring will be determined by the Sponsor Medical Monitor in consultation with the Investigator.

The final study visit will be the Week 26/ET Visit.

3.5. End-of-Study

The End-of-Study is defined as the date of the last visit of the last patient in the study.

3.6. Data and Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) will be assembled to review safety, tolerability, and efficacy (as needed) data collected on ISIS 721744 during this study. Based on its ongoing assessment of the safety and tolerability of ISIS 721744, the DSMB will provide recommendations to the Sponsor for modifying, stopping, or continuing the study as planned. Details on the safety assessments, frequency of review, meeting schedules, and controlled access to unblinded data are outlined in the DSMB Charter and Statistical Analysis Plan (SAP).

4. PATIENT ENROLLMENT

4.1. Screening

Before patients may be enrolled into the study, the Sponsor or designee requires a copy of the Study Center's written Independent Ethics Committee (IEC)/Institutional Review Board (IRB) approval of the protocol, informed consent form (ICF), and all other patient information and/or recruitment material.

Patients must sign the consent form before any screening tests or assessments, including fasting prior to screening blood draws, are performed. At the time of consent, the patient will be considered enrolled into the study and will be assigned a unique screening number before any study procedures, including screening procedures, are performed. At the time of randomization, patients will be assigned a unique patient identification number. This number will be used to identify the patient throughout the study and must be used on all study documentation related to that patient. The screening number and patient identification number must remain constant throughout the entire study.

In the event the patient is re-consented and re-screened, the patient must be given a new screening number. Screening numbers, once assigned, will not be re-used.

4.2. Randomization

Patients will be allocated into Part A or Part B according to type of HAE (i.e., either HAE-1/HAE-2 in Part A or HAE-nC1-INH in Part B). Only Part A will be randomized and placebo-controlled.

Patients will be enrolled and/or randomized (Part A only) at the Week 1 Visit, after all screening assessments have been completed and after the Investigator has verified that they are eligible per the criteria in Sections 5.1 and 5.2. No patient may begin treatment prior to randomization (Part A only) and assignment of a unique patient identification number.

In Part A, approximately 18 patients with HAE-1/HAE-2 will be randomized via the Interactive Response Technology (IRT) system to SC injections of ISIS 721744 80 mg or placebo in a 2:1 ratio (ISIS 721744:placebo). In Part B, approximately 6 patients with HAE-nC1-INH will be enrolled via the IRT system to receive open-label SC injections of ISIS 721744 80 mg. Due to the rarity of HAE-nC1-INH, enrollment in Part B may be ended early if Study Centers are unable to enroll sufficient patients; this will not impact the completion of Part A.

Randomization information will be concealed from the Investigators and patients until the end of the study, with the exception of an emergency situation involving a patient that requires unblinding of the treatment assignment.

Both ISIS 721744 and placebo will be provided as injections for SC administration and will be identical in appearance.

4.3. Replacement of Patients

Patients who withdraw from the study will not be replaced.

Patients whose randomization code has been broken will not be replaced.

4.4. Unblinding of Treatment Assignment

For Part A, the Sponsor and all patients, monitors, and Study Center personnel related to the study will be blinded throughout the study. However, if a patient has suffered an SAE (as defined in Section 9.3.3), and/or when knowledge of the treatment assignment will impact the clinical management of the patient, the Investigator will have the ability to unblind the treatment assignment for that patient via the IRT system.

In the case of unblinding, the IRT system will send a blinded notification to the Sponsor or designee within 24 hours to let them know that a patient was unblinded. In addition, all suspected unexpected serious adverse reactions (SUSARs) will be unblinded by the Sponsor or designee for the purpose of regulatory reporting (see Section 9.2).

Every reasonable attempt should be made to complete the ET study procedures and observations (see Appendix A) prior to unblinding, as knowledge of the treatment arm could influence patient assessment.

5. PATIENT ELIGIBILITY

To be eligible to participate in this study candidates must meet the following eligibility criteria within 8 weeks (56 days) of the Week 1 Visit (Study Day 1) or at the time point specified in the eligibility criteria listed.

5.1. Inclusion Criteria

1. Patients must provide written informed consent (signed and dated) and any authorizations required by local law and be able to comply with all study requirements for the duration of the study.
2. Patients must be aged ≥ 18 years at the time of informed consent.

3. Patients must have a documented diagnosis of HAE-1/HAE-2 (for inclusion in Part A) or HAE-nC1-INH (for inclusion in Part B) as defined below:
   a. Documented diagnosis of HAE-1/HAE-2 based upon ALL of the following:
      i. Documented clinical history consistent with HAE (SC or mucosal, non-pruritic swelling episodes without accompanying urticaria) (Maurer et al. 2018).
      ii. Diagnostic testing results that confirm HAE-1/HAE-2: C1-INH functional level < 40% normal level. Patients with a functional level of 40% to 50% of normal can be enrolled if their complement factor C4 (C4) level is below the LLN or if a known pathogenic mutation in the *SERPING1* gene has been demonstrated.
      iii. At least 1 of the following: age at reported HAE onset ≤ 30 years; a family history consistent with HAE-1/HAE-2; or complement component 1q within the normal range.
   b. Documented diagnosis of HAE-nC1-INH based upon documented clinical history consistent with HAE (SC or mucosal, non-pruritic swelling episodes without accompanying urticaria) (Maurer et al. 2018) AND any 1 of the following:
      i. A clinical diagnosis of BK-mediated angioedema as confirmed with threshold-stimulated kallikrein activity and Investigator-confirmed response to acute use of a BK targeted treatment (icatibant or ecallantide).
      ii. One (1) of the established mutations (c.1032C>A, Thr309Lys; c.1032C>G, Thr309Arg; c.971_1018+24del72*; or c.892_909dup) in the factor XII gene.
      iii. The established mutation in the plasminogen gene (c.9886A>G, p.Lys330Glu).
      iv. The established mutation in the angiopoietin-1 gene (c.807G>T, p.A119S).
4. Patients must experience a minimum of 2 HAE attacks (assessed by the Angioedema Activity Score [AAS] and confirmed by the Investigator) during the Screening Period.
5. Patients must have access to, and the ability to use, ≥ 1 acute medication(s) (e.g., plasma-derived or recombinant C1-INH concentrate or a BK2-receptor antagonist) to treat angioedema attacks.
6. Female patients must be non-pregnant (and not planning a pregnancy during the study) and non-lactating, and be either:
   a. Surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, or bilateral oophorectomy).
   b. Post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years of age, 12 months of spontaneous amenorrhea without an alternative medical cause and follicle-stimulating hormone [FSH] levels in the post-menopausal range for the laboratory involved).
   c. Abstinent (only acceptable as true abstinence, i.e., when in line with the preferred and usual lifestyle of the patient; periodic abstinence [e.g., calendar, ovulation, symptothermal, or post-ovulation methods], declaration of abstinence for the duration of the study, or withdrawal are not acceptable methods of contraception).

d. If engaged in sexual relations of childbearing potential, agree to use highly effective contraceptive methods (refer to Section 6.3.1) from the time of signing the ICF until at least 13 weeks after the last dose of Study Drug (ISIS 721744 or placebo).

7. Male patients must be surgically sterile or, if engaged in sexual relations with a female of childbearing potential, the patient must agree to use an acceptable contraceptive method (refer to Section 6.3.1) from the time of signing the ICF until at least 13 weeks after the last dose of Study Drug (ISIS 721744 or placebo).

5.2. Exclusion Criteria

1. Anticipated use of short-term prophylaxis for angioedema attacks for a pre-planned procedure during the Screening or Study Periods.
2. Concurrent diagnosis of any other type of recurrent angioedema, including acquired or idiopathic angioedema.
3. Anticipated change in the use of concurrent androgen prophylaxis used to treat angioedema attacks.
4. Any clinically-significant abnormalities in screening laboratory values that would render a patient unsuitable for inclusion in the study. The following values are exclusionary:
   a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.5 x upper limit of normal (ULN).
   b. Bilirubin > 1.5 x ULN unless due to Gilbert's syndrome.
   c. Platelet count < LLN.
   d. Estimated glomerular filtration rate (eGFR) < 60 mL/min (as determined by the Cockcroft-Gault Equation for creatinine clearance).
5. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to dosing.
6. Known history of or positive test for human immunodeficiency virus (HIV), hepatitis C, or chronic hepatitis B.
7. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma in situ of the cervix that has been successfully treated.
8. Treatment with another investigational drug or biological agent within 1 month or 5 half-lives, whichever is longer, of Screening.
9. Exposure to any of the following medications:
   a. Angiotensin-converting enzyme (ACE) inhibitors or any estrogen-containing medications with systemic absorption (such as oral contraceptive or hormonal replacement therapy) within 4 weeks prior to Screening.
   b. Chronic prophylaxis with Lanadelumab within 6 months prior to Screening.
   c. Oligonucleotides (including small interfering RNA) within 4 months of Screening if single dose received, or within 12 months of Screening if multiple doses received.

10. Any condition that, in the opinion of the Investigator, may compromise the patient's safety or compliance, preclude successful conduct of the study, or interfere with the interpretation of results.

6. STUDY PROCEDURES

6.1. Study Schedule

The study will be conducted concurrently in 2 parts (Part A and Part B); patients will be allocated into Part A or Part B according to type of HAE (i.e., either HAE-1/HAE-2 in Part A or HAE-nC1-INH in Part B). Part A is randomized, double-blind, and placebo-controlled; and Part B is open label. The study visit schedule and procedures are nearly identical in Part A and Part B, and thus are presented together; any differences are indicated where applicable.

All required study procedures are outlined in Appendix A.

The safety of ISIS 721744 will be continually monitored throughout the study by the Investigator and the Sponsor Medical Monitor.

The length of each patient's participation from Screening to the last study visit is up to approximately 8 months (231 days).

6.1.1. Screening

Written informed consent for the study will be obtained prior to the performance of any study-related procedures, including screening procedures. A 56-day period is provided for completing screening assessments and determining patient eligibility for the study.

Safety labs may be retested for determination of patient eligibility at the Investigator's discretion. The Sponsor Medical Monitor will be available for consultation, if needed.

After providing written informed consent, patients will be screened for eligibility criteria. During the Screening Period, the following assessments will be performed: demographics; medical history, including a detailed HAE history; prior and concomitant medications, including type of prophylaxis (if used) and type of acute treatment; HIV, hepatitis B, and hepatitis C screening; pregnancy testing for women of childbearing potential (WOCBP) and FSH testing for post-menopausal women; quality of life as assessed by the AE-QoL questionnaire; attack frequency, as assessed by the AAS daily during up to 8 consecutive weeks, and confirmed by the Investigator; HAE attack assessment; physical examinations, including vital signs, body height, and weight; ECGs; AEs; PD blood sampling; inflammatory panel; and clinical laboratory assessments (chemistry, hematology, coagulation, and urinalysis).

Threshold-stimulated kallikrein activity will be assessed only in patients who have HAE-nC1-INH without a factor XII mutation or the plasminogen or angiopoietin-1 mutation. Genetic testing will be performed only for patients who do not have HAE genetic diagnostic testing results prior to Screening. During the Screening Period, patients must experience a minimum of 2 HAE attacks (assessed by the AAS and confirmed by the Investigator) to be eligible for the study; patients will be instructed to report details of any HAE attack to the study site within 72 hours of the onset of the attack. Throughout the Screening Period, site personnel

will contact the patient once a week (at approximately 7 days after the last contact with the patient) in order to solicit for any attack that may have occurred. If a patient experiences a third attack, the patient should be randomized as soon as possible, assuming all other screening activities have been completed and the patient meets all other eligibility requirements; in such cases, the Screening Period may be shorter than 8 weeks.

During the course of the study, the use of acute medications (plasma-derived or recombinant C1-INH concentrate, BK2-receptor antagonist, or kallikrein inhibitor) to treat angioedema attacks is allowed as medically indicated. Patients can be treated with on-demand therapy as determined by their treating physician.

6.1.2. Treatment Period

After a Screening Period of up to 8 weeks, those patients who had at least 2 documented attacks (assessed by the AAS and confirmed by the Investigator) during the Screening Period and met all other eligibility criteria will be administered Study Drug (ISIS 721744 or placebo). Patients in Part A will be randomized to receive ISIS 721744 80 mg or placebo every 4 weeks for a total Treatment Period of 12 weeks. Patients in Part B will all receive open-label ISIS 721744 80 mg every 4 weeks for a total Treatment Period of 12 weeks.

The first dose of Study Drug will be administered at the Study Center on Study Day 1 (Week 1 Visit). ISIS 721744 will be administered as SC injections in the abdomen, thigh, or outer area of the upper arm. The following study visits will occur during the Treatment Period: Week 1 (Administration 1), Week 3 (safety monitoring), Week 5 (Administration 2), Week 9 (Administration 3), and Week 13 (Administration 4). A ± 2-day excursion from the scheduled visit date is permitted for all visits (excluding the Week 1 Visit on Study Day 1) during the Treatment Period.

During the study, patients will be instructed to report details of any HAE attack to the study site within 72 hours of the onset of the attack. During the Treatment Period, the following data will be collected: daily AAS and number of HAE attacks (assessed by the AAS and confirmed by the Investigator); number of HAE attacks that required on-demand treatment; HAE attack details, including localization, severity, course, and details of any required treatment (i.e., frequency and dose); and vital signs. Throughout the Treatment Period, site personnel will contact the patient once a week (at approximately 7 days after the last contact with the patient) in order to solicit for any attack that may have occurred. In addition, during study visits, site personnel will solicit for any new HAE attack information that was not provided through patient contact with the site. See Section 6.2.1 for further information on the collection of data surrounding HAE attacks. Additional assessments will be performed throughout the Treatment Period as indicated in the Schedule of Procedures table in Appendix A.

Additionally, blood will be collected to assess PD and coagulation parameters, including, but not limited to: plasma PKK, plasma proenzyme activation, cHK levels, D-dimer levels, aPTT, plasmin-antiplasmin complexes, C4 split products, and platelet counts. Blood samples will also be collected regularly throughout the study for safety and PK/PD analyses.

Patients who discontinue treatment will remain in the study and attend the ET Visit unless consent is withdrawn.

Detailed information regarding the study procedures is presented in Section 6 and Appendix A. Appendix B includes a list of laboratory analytes required for the study.

6.1.3. Post-Treatment Period

Each patient will be followed for safety assessments for up to 13 weeks after the last dose of Study Drug. During the Post-Treatment Period, patients will return to the Study Center for visits at Weeks 17, 21, and 26/ET for safety and clinical laboratory evaluations and for blood sampling for PK/PD analyses. A ± 2-day excursion from the scheduled visit date is permitted for the visits at Weeks 17 and 21, and a ± 3-day excursion from the scheduled visit date is permitted for the visit at Week 26/ET.

During the Post-Treatment Period, the following data will be collected: daily AAS and number of HAE attacks (assessed by the AAS and confirmed by the Investigator); number of HAE attacks that required on-demand treatment; HAE attack details, including localization, severity, course, and details of any required treatment (i.e., frequency and dose); and vital signs. Throughout the Post-Treatment Period, site personnel will contact the patient once a week (at approximately 7 days after the last contact with the patient) in order to solicit for any attack that may have occurred. In addition, during study visits, site personnel will solicit for any new HAE attack information that was not provided through patient contact with the site. See Section 6.2.1 for further information on the collection of data surrounding HAE attacks.

Additionally, blood will be collected to assess PD and coagulation parameters, including, but not limited to: plasma PKK, plasma proenzyme activation, cHK levels, D-dimer levels, aPTT, plasmin-antiplasmin complexes, C4 split products, and platelet counts. Blood samples will also be collected regularly throughout the study for safety and PK/PD analyses. Additional assessments will be performed throughout the Post-Treatment Period as indicated in the Schedule of Procedures table in Appendix A.

Patients who withdraw early from the study during the Treatment Period will be required to complete their End-of-Study evaluations following procedures listed for the Week 26/ET Visit; see Appendix A.

6.2. Study Assessments

6.2.1. Collection of Hereditary Angioedema Attack Details

Historical HAE attack information will be collected at Screening. During the study, patients will be instructed to report details of any HAE attack to the study site within 72 hours of the onset of the attack. Throughout the Screening, Treatment, and Post-Treatment Periods, site personnel will contact the patient once a week (at approximately 7 days after the last contact with the patient) in order to solicit for any attack that may have occurred. In addition, during study visits, site personnel will solicit for any new HAE attack information that was not provided through patient contact with the site.

During the Screening, Treatment, and Post-Treatment Periods, detailed information on each HAE attack will be collected, and the number of HAE attacks that required on-demand treatment, and the details of any on-demand treatment used (frequency and dosing), will be assessed. For each HAE attack, the following data will be collected:

- Date/time of symptom onset
- Description of symptoms
- Location of symptoms:
  - Peripheral angioedema: cutaneous swelling involving an extremity, face, neck, torso, and/or genitourinary region
  - Abdominal angioedema: abdominal pain, with or without abdominal distension, nausea, vomiting, or diarrhea
  - Laryngeal angioedema: stridor, dyspnea, difficulty speaking, difficulty swallowing, throat tightening, or swelling of the tongue, palate, uvula, or larynx
- Impact of HAE attack on activity level
- HAE attack severity:
  - Mild: transient or mild discomfort
  - Moderate: mild to moderate limitation in activity, some assistance needed
  - Severe: marked limitation in activity, assistance required
- Need for assistance, medical intervention, emergency room visit, or hospitalization
- Medications to treat the attack
- HAE attack course, including if the HAE attack(s) in question was a typical attack for the patient, or if there was an alternative diagnosis
- Date/time symptoms resolved

6.2.2. Patient-Reported Outcomes

6.2.2.1. Angioedema Quality of Life Questionnaire

Quality of life will be assessed by the AE-QoL questionnaire during Screening and at Weeks 1, 9, 17, and 26/ET.

The AE-QoL questionnaire is a validated tool to assess symptom-specific health-related quality of life impairment in patients suffering from recurrent angioedema (Weller et al. 2013). The AE-QoL is a self-administered questionnaire that can be completed in less than 5 minutes; it comprises 17 questions across 4 domains: functioning, fatigue/mood, fears/shame, and food. The AE-QoL can be used to calculate scores for the 4 individual domains, and can also be used to determine a total score.

6.2.2.2. Angioedema Activity Score

Patients will be instructed on the use of the AAS questionnaire during Screening and will record their HAE attacks using the AAS questionnaire during the Screening Period to confirm study eligibility. The AAS questionnaire will be completed by patients on a daily basis (minimum of 4 daily assessments per week) for the duration of the study.

During the Screening Period, patients must experience a minimum of 2 HAE attacks (assessed by the AAS and confirmed by the Investigator) to be eligible for the study.

Enrolled patients will continue to record HAE attacks using the AAS questionnaire throughout the Treatment and Post-Treatment Periods.

The AAS is a validated patient-reported outcome instrument to assess disease activity in patients with recurrent angioedema. The AAS was designed as a diary-type tool, and is easy to administer and fast to complete. Using the AAS questionnaire, patients score each of 5 key symptom-related factors from 0 to 3, resulting in a total daily score of 0 to 15. Daily AAS can be summed to provide scores every 7 days, every 4 weeks, and every 12 weeks (Weller et al. 2013).

6.2.3. Laboratory Assessments

Laboratory analyte samples will be collected throughout the study. A list of these analytes is contained in Appendix B. Fasted chemistry samples should be taken after fasting for at least 8 hours. During this time, the patient can drink water and should ensure they consume sufficient water in order to avoid dehydration.

If the platelet value, serum creatinine, or liver enzyme tests are uninterpretable (e.g., due to clumping, hemolysis, or quantity not sufficient) or missing, a repeat blood specimen should be re-drawn as soon as possible (ideally within 7 days).

6.3. Restriction on the Lifestyle of Patients

6.3.1. Contraception Requirements

All male patients and WOCBP must refrain from sperm/egg donation and either be abstinent† or use highly effective contraception from the time of signing the ICF until at least 13 weeks after their last dose of Study Drug.

For male patients engaged in sexual relations with a WOCBP, either the patient or their female partner must use highly effective contraception from the time of signing the informed consent until 13 weeks after the patient's last dose of study treatment.

For the purposes of this study, a WOCBP is defined as any female who has experienced menarche, and who does not meet one of the following conditions:

- Post-menopausal: 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the post-menopausal range for the laboratory involved
- 6 weeks after surgical bilateral oophorectomy with or without hysterectomy
- Post-hysterectomy

For the purposes of the study, highly effective contraception is defined as follows:

For male patients:

- Highly effective male contraception includes a vasectomy with negative semen analysis at follow-up, or the non-pregnant female partner of childbearing potential uses a highly effective contraceptive method (defined below).
- Male patients with partners that are pregnant must use condoms as contraception to ensure that the fetus is not exposed to the Study Drug.

For female patients and female partners of male patients, highly effective contraception methods comprise:

- Surgical sterilization (i.e., bilateral tubal occlusion); progestogen-only hormonal contraception associated with inhibition of ovulation; intrauterine contraception device or intrauterine hormone-releasing system.

†**Note:** Abstinence (i.e., refraining from heterosexual intercourse throughout the duration of study participation) is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods), declaration of abstinence for the duration of the study, or withdrawal are not acceptable methods of contraception.

Note: A female condom and a male condom should not be used together as friction between the two can result in either or both products failing.

6.3.2. Other Requirements

All patients will be required to fast for at least 8 hours before visits that require fasted blood sampling. During this time, the patient can drink water and should ensure they consume sufficient water in order to avoid dehydration.

7. STUDY DRUG

7.1. Study Drug Description

Study Drug (ISIS 721744 or placebo) characteristics are listed in Table 1.

The Study Drug (ISIS 721744 or placebo) is contained in 2-mL stoppered glass vials. The Study Drug (ISIS 721744 or placebo) and its storage and preparation instructions will be provided by the Sponsor or designee. The Study Drug (ISIS 721744 or placebo) must be stored securely at 2 °C to 8 °C and be protected from light.

During the Treatment Period, Study Drug (ISIS 721744 or placebo) will be administered as a single-SC injection every 4 weeks during on-site study visits.

Table 1: Study Drug Characteristics

Study Drug	ISIS 721744	Placebo
Strength	100 mg/mL	Not Applicable
Volume/Formulation	0.8 mL solution per vial	0.8 mL solution per vial
Route of Administration	SC	SC

7.2. Packaging and Labeling

The Sponsor will provide the Investigator with packaged Study Drug (ISIS 721744 or placebo) labeled in accordance with specific country regulatory requirements.

7.3. Study Drug Accountability

The study staff is required to document the receipt, dispensing, and return/destruction of Study Drug (ISIS 721744 or placebo) supplies provided by the Sponsor according to Sponsor instruction and in accordance with institutional policy.

8. TREATMENT OF PATIENTS

8.1. Study Drug Administration

Study Drug (ISIS 721744 or placebo) will be administered as a single-SC injection once every 4 weeks by blinded study staff during on-site visits at the Study Centers. Vials of Study Drug (ISIS 721744 or placebo) are for single use only.

Please refer to the Study Drug Manual provided by the Sponsor or designee for more detailed instructions for Study Drug (ISIS 721744 or placebo) preparation and administration.

8.2. Other Protocol-Required Drugs

Patients must have access to, and the ability to use, ≥ 1 acute medication(s) (e.g., plasma-derived or recombinant C1-INH concentrate or a BK2-receptor antagonist) to treat angioedema attacks. During the course of the study, the use of acute medications (plasma-derived or recombinant C1-INH concentrate, BK2-receptor antagonist, or kallikrein inhibitor) to treat angioedema attacks is allowed as medically indicated. Patients can be treated with on-demand therapy as determined by their treating physician.

8.3. Other Protocol-Required Treatment Procedures

There are no other protocol-required treatment procedures.

8.4. Treatment Precautions

There are no specific treatment precautions required.

8.5. Safety Monitoring Rules

Please refer also to the "Guidance for Investigator" section of the Investigator's Brochure.

For the purposes of safety monitoring, Baseline is defined as the average of the pre-dose Study Day 1 value and the last value prior to Study Day 1.

In addition to the standard monitoring of clinical safety parameters, the following guidelines are provided for the monitoring of selected parameters chosen based on preclinical and clinical observations.

Confirmation Guidance: At any time during the study (Treatment or Post-Treatment Periods), the initial clinical laboratory results meeting the safety monitoring criteria presented below **must be confirmed** by performing measurements (ideally in the same laboratory that performed the initial measurement) on new specimens. All new specimen collections should take place as soon as possible (ideally within 3 days of the initial collection). For stopping rules, if the initial laboratory result is observed during the Treatment Period, the results from the retest **must be available** prior to administering the next dose of Study Drug (ISIS 721744 or placebo).

Re-dosing Guidance: Patients with initial laboratory test values that reach a stopping rule must not be re-dosed until the retest results are available. In general, patients who do not meet the stopping rules based upon retest may continue dosing. However, the Investigator and the Sponsor Medical Monitor (or appropriately qualified designee) should confer as to whether additional close monitoring of the patient is appropriate. If any of the stopping criteria described below (refer to Section 8.6) are met, the patient will be permanently discontinued from further treatment with Study Drug (ISIS 721744 or placebo), evaluated fully as outlined below and in consultation with the Sponsor Medical Monitor or appropriately qualified designee, and will be followed up in accordance with Section 8.8 of the protocol.

8.5.1. Safety Monitoring Rules for Liver Chemistry Tests

The following rules are adapted from the draft guidance for industry, "Drug-Induced Liver Injury: Premarketing Clinical Evaluation," issued by the U.S. Department of Health and Human Services, Food and Drug Administration, July 2009. For a definition of Baseline, please refer to guidance in Section 8.5 above.

In the event of an ALT or AST measurement that is > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN) at any time during the study (Treatment or Post-Treatment Period), the initial measurement(s) should be confirmed as described above. Additional, confirmatory measurements should also be performed if ALT or AST levels increase to 5 x ULN.

Frequency of Repeat Measurements: Patients with confirmed ALT or AST levels > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN) should have their liver chemistry tests (ALT, AST, alkaline phosphatase, international normalized ratio [INR], and total bilirubin) retested at least once-weekly until ALT and AST levels become ≤ 1.2 x ULN or 1.2 x baseline value if the baseline value was > ULN.

Further Investigation into Liver Chemistry Elevations: For patients with confirmed ALT or AST levels > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), the following evaluations should be performed:

- Obtain a more detailed history of symptoms and prior and concurrent diseases
- Obtain further history for concomitant drug use (including non-prescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
- Obtain a history for exposure to environmental chemical agents and travel
- Perform serology for viral hepatitis (hepatitis A virus immunoglobulin M ([IgM], hepatitis B surface antigen, hepatitis C virus antibody, cytomegalovirus IgM, and Epstein-Barr Virus antibody panel)
- Perform serology for autoimmune hepatitis (e.g., antinuclear antibody)

Additional liver evaluations, including gastroenterology/hepatology consultations, hepatic computed tomography or magnetic resonance imaging scans, may be performed at the discretion of the Investigator, in consultation with the Sponsor Medical Monitor. Repetition of the above evaluations should be considered if a patient's ALT and/or AST levels reach 5 x ULN.

8.5.2. Safety Monitoring Rules for Platelet Count Results

Please refer also to Table 2.

Platelet count will be monitored at least every 4 weeks during the Treatment and Post-Treatment Periods. The Investigator should review all platelet count results within 48 hours of receipt. Any unreportable platelet count result must be rechecked ideally within 7 days and determined not to have met a stopping rule before dosing can continue. If a patient's platelet count falls to 100,000/mm^3 or less, then the patient's platelet counts should be monitored weekly. In case of platelet reduction to below 75,000/mm^3, the platelet monitoring rule defined in stopping rules (Section 8.6.2) should be followed.

In the event of a platelet count < 75,000/mm^3, additional laboratory investigations may be conducted in consultation with the Sponsor Medical Monitor.

8.5.3. Safety Monitoring Rules for Renal Function Test Results

If a patient's results meet Criteria 1 or 2 below, the Investigator should confirm the results and initiate weekly monitoring if confirmed. If the event of a persistent elevation is observed over 2 consecutive weeks, then go to Section 8.6.3.

1. Serum creatinine increase that fulfills all of the following: ≥ 0.3 mg/dL (26.5 µmol/L) and ≥ 40% above baseline creatinine values and > ULN (refer to definition of Baseline in Section 8.6)
2. Proteinuria, urine protein/creatinine ratio > 750 mg/g for baseline values > 200 mg/g, or 4 x baseline value for baseline values < 200 mg/g that are confirmed by repeated urine protein/creatinine ratio or by a quantitative total urine protein measurement of > 1.0 g/24 hours

8.5.4. Safety Monitoring for Minor Bleeding Events

If a bleeding event occurs, including minor bleeding events such as excess bruising, petechiae, or gingival bleeding on brushing teeth, the Investigator should notify the Sponsor Medical Monitor and additional testing of coagulation parameters (aPTT, PT, and INR) and platelet count should be performed.

8.6. Stopping Rules

For the purposes of the stopping rules, Baseline is defined as the average of the pre-dose Study Day 1 value and the last value prior to Study Day 1.

8.6.1. Stopping Rules for Liver Chemistry Elevations

In the event of laboratory results meeting the following criteria, **and the event is without an alternative explanation as discussed with the Sponsor Medical Monitor,** dosing of a patient with Study Drug (ISIS 721744 or placebo) will be stopped permanently; values that are not confirmed due to failure to retest or missing lab values will be presumed confirmed:

1. ALT or AST > 8 x ULN, which is confirmed
2. ALT or AST > 5 x ULN, which is confirmed and persists for ≥ 2 weeks
3. ALT or AST > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), which is confirmed **and** total bilirubin > 1.5 x ULN or INR > 1.5
4. ALT or AST > 3 x ULN (or the greater of 2 x baseline value or 3 x ULN if the baseline value was > ULN), which is confirmed, **and** the new appearance (i.e., onset coincides with the changes in hepatic enzymes) of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or concomitant eosinophilia (> ULN)

8.6.2. Stopping Rules for Platelet Count Results

Please refer also to Table 2.

In the event of any platelet count < 25,000/mm^3, dosing of the patient with Study Drug will be stopped permanently. Platelet count should be monitored daily until 3 successive values > 25,000/mm^3. Then, monitor twice weekly until 3 successive values > 75,000/mm^3. Then, monitor weekly until 3 successive values > 100,000/mm^3. Consider more frequent monitoring if additional risk factors for bleeding are present (see Table 2). Administration of steroids is strongly recommended for patients whose platelet count is < 25,000/mm^3. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend dexamethasone 40 mg daily for 4 days every 2 to 4 weeks for 1 to 4 cycles; prednis(ol)one 0.5 to 2 mg/kg/day for 2 to 4 weeks then taper; or methylprednisolone 30 mg/kg/day for 7 days. (**Note:** Patient may require continuation with oral steroids after methylprednisolone).

In the event of a platelet count ≥ 25,000/mm^3 to < 50,000/mm^3, dosing of the patient with Study Drug will be stopped permanently. Platelet count should be monitored twice weekly until 3 successive values > 75,000/mm^3. Then, monitor weekly until 3 successive values > 100,000/mm^3. Consider more frequent monitoring and/or the administration of steroids if additional risk factors for bleeding are present (see Table 2).

In the event of a platelet count ≥ 50,000/mm^3 to < 75,000/mm^3, and in the absence of major bleeding or clinically-relevant non-major bleeding (defined below), dosing with Study Drug should be suspended temporarily until the platelet count has recovered to > 100,000/mm^3. The suitability of the patient for continued dosing will be determined by the Investigator in consultation with the Sponsor Medical Monitor and will be based on factors such as the original rate of decline in the patient's platelet count, whether any bleeding events were experienced, and the speed of recovery of platelet count after interruption of dosing. Platelet count must be measured twice weekly until 3 successive values > 75,000/mm^3, then weekly until 3 successive values > 100,000/mm^3. Consider more frequent monitoring if additional risk factors for bleeding are present (see Table 2). Any unreportable platelet count result must be rechecked, ideally within 7 days, and determined not to have met a stopping rule before dosing can continue.

Definition of Major Bleeding Events (Schulman and Kearon 2005)

1. Fatal bleeding, and/or
2. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarterial or pericardial, or intramuscular with compartment syndrome, and/or
3. Clinically overt bleeding leading to transfusion of ≥ 2 units of packed red blood cells or whole blood or a fall in hemoglobin of ≥ 2.0 mg/dL (1.24 mmol/L) within 24 hours

Definition of Clinically-Relevant Non-Major Bleeding Events

Clinically-relevant non-major bleeding is defined as overt bleeding not meeting the criteria for major bleeding but that resulted, for example, in medical examination, intervention, or had clinical consequences for a patient.

Definition of Minor Bleeding Events

Minor bleeding events are those that do not fulfill the criteria for major bleeding or clinically-relevant, non-major bleeding events (defined above), for example excess bruising, petechiae, or gingival bleeding on brushing teeth.

If the subsequent test confirms the initial test result, then monitoring frequency and dosing should be adjusted as recommended in Table 2.

Table 2: Actions in Patients with Low Platelet Count

Platelet count (/mm^9)	Dosing	Monitoring frequency
> 100	Dosing every 4 weeks should be continued.	At least every 4 weeks.
≥ 75 to ≤ 100	Dosing every 4 weeks should be continued.	Every week.
≥ 50 to < 75	Pause dosing. When platelet count returns to > 100/mm^9, restart dosing only if approved by the Sponsor Medical Monitor.	Twice weekly until 3 successive values > 75/mm^9, then weekly until 3 successive values > 100/mm^9. Consider more frequent monitoring if additional risk factors for bleeding are present.‡
≥ 25 to < 50	Permanently discontinue Study Drug. Consider corticosteroids if additional risk factors for bleeding are present.‡	Twice weekly until 3 successive values > 75/mm^9, then weekly until 3 successive values > 100/mm^9. Consider more frequent monitoring if additional risk factors for bleeding are present.‡
< 25	Permanently discontinue Study Drug. Corticosteroids strongly recommended.*	Daily until 3 successive values > 25/mm^9, then twice weekly until 3 successive values > 75/mm^9, then weekly until 3 successive values > 100/mm^9. Consider more frequent monitoring if additional risk factors for bleeding are present.‡

‡ Additional risk factors for bleeding include age > 60 years, receiving anticoagulant or antiplatelet medicinal products, and/or prior history of major bleeding events.

* It is strongly recommended that, unless corticosteroids are contraindicated, the patient receives glucocorticoid therapy to reverse the platelet decline as recovery in platelet count may be accelerated by administration of high-dose steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend dexamethasone 40 mg daily for 4 days every 2 to 4 weeks for 1 to 4 cycles; prednis(ol)one 0.5 to 2 mg/kg/day for 2 to 4 weeks then taper; or methylprednisolone 30 mg/kg/day for 7 days (**Note:** patient may require continuation with oral steroids after methylprednisolone).

8.6.3. Temporary Stopping Rules for Renal Function Test Results

In the event of a persistent elevation that is observed over 2 consecutive weeks, for either of the 2 criteria below, dosing of a patient with Study Drug (ISIS 721744 or placebo) may be stopped temporarily:

1. Serum creatinine increase that fulfills all of the following criteria: ≥ 0.3 mg/dL (26.5 µmol/L) and ≥ 40% above baseline creatinine values and > ULN (refer to definition of Baseline in Section 8.6)

2. Proteinuria, dipstick 2 + (confirmed by dipstick retest and then further confirmed by a quantitative total urine protein measurement of > 1.0 g/24 hours)

The possible dosing reinitiation or follow-up schedule for any events meeting either of these criteria will be determined by the Investigator **in consultation with** the Sponsor Medical Monitor or designee.

8.7. Adjustment of Dose and/or Treatment Schedule

Adjustment of dose and/or schedule is not permitted.

8.8. Discontinuation of Study Drug

A patient must permanently discontinue study treatment for any of the following:

- The patient becomes pregnant. Report the pregnancy according to instructions in Section 9.5.4.
- The patient withdraws consent.
- The patient withdraws from treatment (but does not withdraw consent).
- The patient experiences an AE that necessitates permanent discontinuation of Study Drug.
- The patient develops laboratory test abnormalities that meet any of the stopping rules listed in Sections 8.6.1, 8.6.2, or 8.6.3.
- The patient experiences an AE that necessitates unblinding of the Investigator or Sponsor to the patient's treatment assignment.

The reason for discontinuation of Study Drug must be recorded in the electronic Case Report Form (eCRF) and source documentation.

Patients who discontinue Study Drug will remain in the study and attend the ET Visit (Week 17 visit assessments), unless consent is withdrawn. Any patient who discontinues early from the Treatment Period or from the Post-Treatment Follow-Up Period should be strongly encouraged to complete follow-up study visits, procedures and observations (see Appendix A).

8.9. Withdrawal of Patients from the Study Procedures

Patients must be withdrawn from study procedures for any of the following:

- Withdrawal of consent
- The patient is unwilling or unable to comply with the protocol

Other reasons for withdrawal of patients from the study may include the following:

- At the discretion of the Investigator for medical reasons
- At the discretion of the Investigator or Sponsor for non-compliance
- Significant protocol deviation

All efforts will be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. All information, including the reason for withdrawal from study, must be recorded in the eCRF.

Any patient who withdraws consent to participate in the study will be removed from further treatment and study observation immediately upon the date of request. These patients should be encouraged to complete the ET study procedures (Week 17 visit assessments) and observations at the time of withdrawal (see Appendix A).

For patients withdrawn for reasons other than withdrawal of consent, every effort should be made to complete the ET study procedures and observations at the time of withdrawal (see Appendix A).

8.10. Concomitant Therapy and Procedures

The use of concomitant therapies or procedures defined below must be recorded on the patient's eCRF. Adverse events related to administration of these therapies or procedures must also be documented on the appropriate eCRF.

8.10.1. Concomitant Therapy

A concomitant therapy is any non-protocol-specified drug or substance (including over-the-counter medications, herbal medications, and vitamin supplements) administered between Screening and the end of the Post-Treatment Period.

Allowed Concomitant Therapy

During the course of the study, the use of acute medications (plasma-derived or recombinant C1-INH concentrate, BK2-receptor antagonist, or kallikrein inhibitor) to treat angioedema attacks is allowed as medically indicated. Patients can be treated with on-demand therapy as determined by their treating physician.

All other stable medications (if not excluded below) are allowed, so long as the dose and type is not expected to change during the study.

Disallowed Concomitant Therapy

1. Chronic prophylaxis for angioedema attacks, except for a stable dose of androgens. Any use of Lanadelumab will not be permitted.

   NOTE: The use of acute medications (plasma-derived or recombinant C1-INH concentrate or BK2-receptor antagonist) to treat angioedema attacks is allowed as medically indicated.

2. ACE inhibitors or any estrogen-containing medications with systemic absorption (such as oral contraceptive or hormonal replacement therapy).
3. Any oligonucleotides (including small interfering RNA) other than ISIS 721744.
4. Plasmapheresis.
5. Any other investigational drug or device.

8.10.2. Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between Screening and the end of the Post-Treatment Period.

8.11. Treatment Compliance

Compliance with treatment dosing is to be monitored and recorded in the eCRF by Study Center staff.

9. SERIOUS AND NON-SERIOUS ADVERSE EVENT REPORTING

9.1. Sponsor Review of Safety Information

Safety information will be collected, reviewed, and evaluated by the Sponsor or designee in accordance with the applicable Ionis and/or designee Standard Operating Procedures throughout the conduct of the clinical study.

9.2. Regulatory Requirements

The Sponsor or designee is responsible for regulatory submissions and reporting to the Investigators of SAEs including SUSARs per the International Council for Harmonisation (ICH) guidelines E2A and ICH Good Clinical Practice (GCP). Country-specific regulatory requirements will be followed in accordance with local country regulations and guidelines.

Institutional Review Boards/IECs will be notified of any SAE according to applicable regulations. The DSMB will be notified of any SAE as specified in the DSMB Charter.

In addition to the Investigator's assessment of relatedness, the Sponsor or designee will evaluate the available information and perform an independent assessment of all reported SAEs and determine if there is a reasonable possibility that the Study Drug (ISIS 721744 or placebo) is causally related to a reported SAE. While the Sponsor may upgrade an Investigator's decision, it is not permissible to downgrade the Investigator's opinion for the purposes of determining whether the SAE meets the definition of a SUSAR.

Appropriate personnel at the Sponsor or designee will unblind SUSARs for the purpose of regulatory reporting. The Sponsor or designee will submit SUSARs to regulatory agencies in blinded or unblinded fashion according to local law. The Sponsor or designee will submit SUSARs to Investigators in a blinded fashion.

9.3. Definitions

9.3.1. Adverse Event

An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the AE is considered related to the medicinal (investigational) product.

An AE can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition)
- Recurrence of an intermittent medical condition (e.g., headache) not present at Baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from Study Drug
- Events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

9.3.2. Adverse Drug Reaction and Unexpected Suspected Adverse Drug Reaction

Adverse Drug Reaction

In the *pre-approval* clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not have been established, adverse drug reactions (ADRs) are defined as follows:

> All noxious and unintended responses to a medicinal product related to any dose should be considered ADRs.

The phrase “responses to a medicinal product” means that a causal relationship between the medicinal product and the AE has been determined by the Sponsor as at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Suspected Unexpected Adverse Drug Reaction

A suspected unexpected ADR is any ADR, the nature or severity of which is not consistent with the applicable product information, e.g., Investigator's Brochure for an unapproved medicinal (investigational) product.

A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

9.3.3. Serious Adverse Event

An SAE is any AE that, in the view of either the Investigator or Sponsor, meets any of the following criteria:

- Results in death
- Is life-threatening; that is, poses an immediate risk of death at the time of the event

  An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization

  Hospitalization is defined as an admission of greater than 24 hours to a medical facility and does not always qualify as an AE
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Results in a congenital anomaly or birth defect in the offspring of the patient (whether the patient is male or female)
- Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may also be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (e.g., rated as mild, moderate, or severe; or according to National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE]); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each AE recorded on the eCRF.

9.4. Monitoring and Recording Adverse Events

Any pre-existing conditions or signs and/or symptoms present in a patient prior to the start of the study (i.e., before informed consent) should be recorded as Medical History and not recorded as AEs unless the pre-existing condition worsened. The Investigator should always group signs and symptoms into a single term that constitutes a **single unifying diagnosis** if possible. Before a diagnosis is confirmed, all symptoms should be reported as separate AEs.

9.4.1. Serious Adverse Events

In the interest of patient safety, and in order to fulfill regulatory requirements**,** all SAEs (regardless of their relationship to Study Drug) should be reported to the Sponsor or designee

within 24 hours of the Study Center's first knowledge of the event. The collection of SAEs will begin after the patient signs the ICF and will stop at the end of the patient's Post-Treatment Period, which is defined as completion of the Week 26/ET Visit. When the Investigator is reporting by telephone, it is important to speak to someone in person vs. leaving a message. Serious adverse events should be reported using an electronic SAE submission form whenever possible. In situations where the electronic SAE submission is unavailable, an Initial Serious Adverse Event Form should be completed and a copy should be faxed or emailed to the Sponsor or designee. The SAE reporting instructions, including the fax number and email address, can be found in the Investigator Site File for the study.

Detailed information should be actively sought and included on Follow-Up Serious Adverse Event Forms as soon as additional information becomes available. All SAEs will be followed until resolution. Serious adverse events that remain ongoing past the patient's last protocol-specified follow-up visit will be evaluated by the Investigator and Sponsor. If the Investigator and Sponsor agree that the patient's condition is unlikely to resolve, the Investigator and Sponsor will determine the follow-up requirement.

9.4.2. Non-Serious Adverse Events

The recording of non-serious AEs will begin after the patient signs the ICF and will stop at the end of the patient's Post-Treatment Period, which is defined as completion of the Week 26/ET Visit. The Investigator will monitor each patient closely and record all observed or volunteered AEs on the eCRF.

9.4.3. Evaluation of Adverse Events (Serious and Non-Serious)

The Investigator's opinion of the following should be documented on the eCRF:

9.4.3.1. Relationship to the Study Drug

The event's relationship to the Study Drug (ISIS 721744 or placebo) is characterized by one of the following:

- **Related:** There is clear evidence that the event is related to the use of Study Drug (ISIS 721744 or placebo), e.g., confirmation by positive re-challenge test
- **Possible:** The event cannot be explained by the patient's medical condition, concomitant therapy, or other causes, and there is a plausible temporal relationship between the event and Study Drug (ISIS 721744 or placebo) administration
- **Unlikely/Remote:** An event for which an alternative explanation is more likely (e.g., concomitant medications or ongoing medical conditions) or the temporal relationship to Study Drug (ISIS 721744 or placebo) administration and/or exposure suggests that a causal relationship is unlikely (for reporting purposes, Unlikely/Remote will be grouped together with Not Related)
- **Not Related:** The event can be readily explained by the patient's underlying medical condition, concomitant therapy, or other causes, and therefore, the Investigator believes no relationship exists between the event and Study Drug (ISIS 721744 or placebo)

9.4.3.2. Severity

The severity of AEs and SAEs relating to laboratory tests and AEs at the injection site will be graded based on criteria from the CTCAE Version 5.0, November 2017 (refer to Appendix D). Any AE not listed in Appendix D will be graded as follows:

- **Mild:** The event is easily tolerated by the patient and does not affect the patient's usual daily activities
- **Moderate:** The event causes the patient more discomfort and interrupts the patient's usual daily activities
- **Severe:** The event is incapacitating and causes considerable interference with the patient's usual daily activities

If the event is an SAE, then all applicable seriousness criteria must be indicated (criteria listed in Section 9.3.3).

9.4.3.3. Action Taken with Study Drug

Down-titration of Study Drug (ISIS 721744 or placebo) will not be allowed during the study.

Action taken with Study Drug (ISIS 721744 or placebo) due to an AE is characterized by one of the following:

- **None:** No changes made to Study Drug (ISIS 721744 or placebo) administration and dose
- **Not Applicable:** AE reported during the Screening Period prior to Study Drug (ISIS 721744 or placebo) administration
- **Permanently Discontinued:** Study Drug (ISIS 721744 or placebo) discontinued and not restarted
- **Temporarily Interrupted, Restarted – Same Dose:** Dosing and/or dosing frequency temporarily interrupted/changed or delayed due to the AE and restarted at the same dose

9.4.3.4. Treatment Given for Adverse Event

Any treatment (e.g., medications or procedures) given for the AE should be recorded on the eCRF. Treatment should also be recorded on the concomitant treatment or ancillary procedures eCRF, as appropriate.

9.4.3.5. Outcome of the Adverse Event

If the event is a non-serious AE, then the event's outcome is characterized by one of the following:

- **AE Persists:** Patient terminates from the study and the AE continues
- **Recovered:** Patient recovered completely from the AE

- **Became Serious:** The event became serious (the date that the event became serious should be recorded as the Resolution Date of that AE and the Onset Date of the corresponding SAE)
- **Change in Severity (if applicable):** AE severity changed

If the event is an SAE, then the event's outcome is characterized by one of the following:

- **Ongoing:** SAE continuing
- **Persists (as non-serious AE):** Patient has not fully recovered but the event no longer meets serious criteria and should be captured as an AE on the non-serious AE eCRF (the SAE resolution date should be entered as the date of onset of that AE)
- **Recovered:** Patient recovered completely from the SAE (the date of recovery should be entered as the SAE resolution date)
- **Recovered with Sequelae:** The signs/symptoms of the reported SAE have improved but not completely resolved, and a new baseline for the patient is established since full recovery is not expected
- **Fatal:** Patient died (the date of death should be entered as the SAE resolution date)
- **Unknown:** The outcome of the reported SAE is not available, e.g., patient is lost to follow-up

9.4.3.6. Follow-up of Adverse Event

Investigator Follow-up

During the Study Period, the Investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all SAEs considered to be related to Study Drug or related to study procedures until a final outcome can be reported.

Resolution of AE (with dates) should be documented on the eCRF and in the patient's medical record to facilitate source data verification.

Investigators should follow-up, or support the Sponsor's effort to follow up, with all pregnancies reported during the study from either the study patient or the female partner of the male study patient until pregnancy outcome is available.

Sponsor Follow-up

For SAEs and pregnancy cases in patients who have completed or terminated the study, the Sponsor or a designee should follow-up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, or autopsy reports) in order to perform an independent medical assessment of the reported case.

9.5. Procedures for Handling Special Situations

9.5.1. Abnormalities of Laboratory Tests

Clinically-significant abnormal laboratory test results may, in the opinion of the Investigator, constitute or be associated with an AE. Examples of these include abnormal laboratory results that are associated with symptoms, or require treatment, e.g., bleeding due to thrombocytopenia, tetany due to hypocalcemia, or cardiac arrhythmias due to hyperkalemia. Whenever possible, the underlying diagnosis should be listed in preference to abnormal laboratory values as AEs. Clinically significant abnormalities will be monitored by the Investigator until the parameter returns to its baseline value or until agreement is reached between the Investigator and Sponsor Medical Monitor. Laboratory abnormalities deemed not clinically-significant (NCS) by the Investigator should not be reported as AEs. Similarly, laboratory abnormalities reported as AEs by the Investigator should not be deemed NCS on the laboratory sheet.

The Investigator is responsible for reviewing and signing all laboratory reports. The signed clinical laboratory reports will serve as source documents and should include the Investigator's assessment of clinical significance of out of range/abnormal laboratory values.

9.5.2. Prescheduled or Elective Procedures or Routinely Scheduled Treatments

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered an SAE, even if the patient is hospitalized; the Study Center must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the patient's consent to participate in the study
- The condition that required the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the Investigator between the patient's consent to participate in the study and the timing of the procedure or treatment
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission

9.5.3. Dosing Errors

Study Drug (ISIS 721744 or placebo) dosing errors (including overdose, underdose, and administration error) should be documented as protocol deviations. A brief description should be provided in the deviation, including whether the patient was symptomatic (list symptoms) or asymptomatic, and the event accidental or intentional.

Dosing details should be captured on the Dosing eCRF. If the patient takes a dose of Study Drug (ISIS 721744 or placebo) that exceeds protocol specifications and the patient is symptomatic, then the symptom(s) should be documented as an AE and be reported per Section 9.4.

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an AE, but it may result in an AE. All AEs associated with an overdose or incorrect administration of Study Drug should be recorded on the Adverse Event eCRF. If the associated AE fulfills seriousness

criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event).

Should an overdose occur, the Investigator or designee should refer to the "Guidance for Investigator" section of the Investigator's Brochure and contact the Sponsor or designee within 24 hours.

9.5.4. Contraception and Pregnancy

Male patients and female patients of childbearing potential must continue to use appropriate contraception with their partners, or refrain from sexual activity, as described in Section 6.3.1.

If a patient becomes pregnant or a pregnancy is suspected, or if a male patient makes or believes that he has made someone pregnant during the study, then the Study Center staff must be informed immediately. An Initial Pregnancy Form should be submitted to the Sponsor or designee **within 24 hours** of first learning of the occurrence of pregnancy. Follow-up information including delivery or termination is reported by designating as 'Follow-up' on the Pregnancy Forms and reported within 24 hours.

Payment for all aspects of obstetrical care, child or related care will be the patient's responsibility.

Female patients: If a suspected pregnancy occurs while on the study (including the Post-Treatment Period), a pregnancy test will be performed. The patient with a confirmed pregnancy will be immediately withdrawn from treatment with Study Drug. However, the patient will be encouraged to complete the Post-Treatment Period of the study to the extent that study procedures do not interfere with the pregnancy. Regardless of continued study participation, the study physician will assist the patient in getting obstetrical care and the progress of the pregnancy will be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, the Study Center and Sponsor may require access to the mother and infant's medical records to obtain additional information relevant to the pregnancy progress and outcome. A longer follow-up may be required if a newborn child experiences a medical condition. Follow-up will be performed to the extent permitted by the applicable regulations and privacy considerations; e.g., pregnancy ICF may be required.

Male patients: The progress of the pregnancy of a male patient's partner should be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, the Study Center and Sponsor may follow-up with the mother and may request access to the mother and infant's medical records to obtain additional information relevant to the pregnancy progress and outcome. A longer follow-up may be required if a newborn child experiences a medical condition. Follow-up will be performed to the extent permitted by the applicable regulations and privacy considerations; e.g., partner ICF may be required.

10. STATISTICAL CONSIDERATIONS

The sections below indicate the overall structure and approach to the analysis of this study. A detailed SAP incorporating these sections below will be prepared separately. The SAP will outline all data handling conventions, including software, and specify additional statistical methods to be used for analysis. The study objectives and endpoints are listed in Sections 1.1 and 1.2, respectively.

10.1. Sample Size Considerations

The study will enroll a total of approximately 24 patients with HAE. Approximately 18 patients with HAE-1/HAE-2 are planned to be enrolled in Part A of the study and, in parallel, approximately 6 patients with HAE-nC1-INH are planned to be enrolled in Part B of the study. Due to the rarity of HAE-nC1-INH, enrollment in Part B may be ended early if Study Centers are unable to enroll sufficient patients; this will not impact completion of Part A. Patients with HAE-1/HAE-2 (Part A) will be randomized to SC injections of ISIS 721744 80 mg or placebo administered every 4 weeks in a 2:1 ratio (ISIS 721744:placebo), and patients with HAE-nC1-INH (Part B) will be administered open-label SC injections of ISIS 721744 80 mg every 4 weeks.

The sample size of 18 patients with HAE-1/HAE-2 (12 patients administered SC injections of ISIS 721744 80 mg and 6 patients administered placebo) is from clinical considerations for sufficient safety and tolerability evaluation. The primary endpoint is the time-normalized number of HAE attacks (per month) from Week 1 to Week 17. From historical data, the placebo group is estimated to have 6.8 HAE attacks per 4-month period. If the ISIS 721744 80 mg group is assumed to have 2.8 HAE attacks per 4-month period, then with a 0.05 significance level and Poisson model, the sample size of 18 patients will provide at least 90% power for the primary endpoint, considering a 10% missing data or dropout rate for both active treatment and placebo. There is no statistical rationale for the sample size of 6 patients with HAE-nC1-INH.

10.2. Populations

The Safety Population will include all enrolled patients who receive at least 1 dose of Study Drug (ISIS 721744 or placebo).

The Intent-to-Treat (ITT) Population will include all enrolled or randomized patients.

The Per-Protocol (PP) Population will include all patients in the ITT Population who are treated according to the protocol without any major deviations.

The PK Population will include all patients who are enrolled and receive at least 1 dose of Study Drug (ISIS 721744 or placebo) and have at least 1 evaluable PK sample.

10.3. Definition of Baseline

For platelets, Baseline will be defined as the average of all non-missing pre-dose assessments.

For other assessments, if there are 2 or more pre-dose values available, Baseline will be defined as the average of the pre-dose Study Day 1 value and the last pre-dose value prior to Study Day 1. If there is only 1 pre-dose measurement available, then it will be assigned as Baseline.

10.4. Data and Safety Monitoring Board

An independent DSMB will be established prior to the initiation of the study. The DSMB will be responsible for monitoring the overall safe conduct of the study. Based on its ongoing assessment of the safety and tolerability of ISIS 721744, the DSMB will provide recommendations to the Sponsor for modifying, stopping, or continuing the study as planned. Details on the safety assessments, frequency of review, meeting schedules and controlled access to unblinded data are outlined in the DSMB Charter and SAP.

10.5. Interim Analysis

No interim analysis is planned for this study.

10.6. Planned Methods of Analysis

10.6.1. Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized using descriptive statistics by treatment group. Patient disposition will be summarized by treatment group. All patients enrolled will be included in a summary of patient disposition.

10.6.2. Safety Analysis

The Safety Population will be used for all safety analyses.

The safety and tolerability of ISIS 721744 will be assessed by determining the number, type, severity, and dose-relationship of AEs; vital signs; ECGs; and clinical laboratory parameters. Safety results in patients dosed with ISIS 721744 will be compared to safety results in patients dosed with placebo.

Treatment duration and amount of Study Drug (ISIS 721744 or placebo) received will be summarized by treatment group. Patient incidence rates of all AEs will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA™) system organ class and by MedDRA term. Tables and/or narratives of treatment-emergent deaths and serious and significant AEs, including early withdrawals due to AEs, will also be provided.

All TEAEs, all TEAEs potentially related to Study Drug, all treatment-emergent SAEs, and all treatment-emergent SAEs potentially related to Study Drug (ISIS 721744 or placebo) will be summarized.

Laboratory tests to ensure patient safety, including chemistry panel, complete blood count with differential, coagulation panel, and complement, will be summarized by study visit for each treatment group. These safety variables will also be presented as change and percent change from Baseline over time after Study Drug (ISIS 721744 or placebo) administration, as appropriate.

Vital sign and ECG measures will be tabulated by treatment group. In addition, the number of patients who experience abnormalities in clinical laboratory evaluations will be summarized by treatment group.

10.6.3. Efficacy Analysis

The ITT Population will be used for all efficacy analyses. The PP Population will be used for a sensitivity analysis to assess robustness of the efficacy analysis results.

10.6.3.1. Primary Efficacy Analysis

The primary endpoint is the time-normalized number of HAE attacks (per month) from Week 1 to Week 17.

The Part A data will be analyzed using a Poisson regression model with treatment group as a fixed effect and the number of baseline HAE attacks as a covariate, and the logarithm of exposure in month will be used as the offset.

The least-squares means, standard errors, and the 2-tailed 95% confidence intervals for the treatment group and placebo group will be presented.

The Part B data will be summarized using descriptive statistics.

10.6.3.2. Secondary Efficacy Analysis

The secondary endpoints include the time-normalized number of HAE attacks (per month) from Week 5 to Week 17 and from Week 9 to Week 21; the time-normalized number of moderate or severe HAE attacks (per month) from Week 5 to Week 17 and from Week 9 to Week 21; the number of patients with a clinical response (defined as a $\geq 50\%$, $\geq 70\%$, or $\geq 90\%$ reduction from Baseline in HAE attack rate) by Week 17; the number of HAE attacks requiring acute therapy from Week 5 to Week 17; cHK levels at Weeks 9 and 17; PKK activity at Weeks 9 and 17; consumption of on-demand medication at Weeks 9 and 17; and AE-QoL questionnaire score at Weeks 9 and 17.

For Part A, the time-normalized number of HAE attacks (per month) from Week 5 to Week 17 and from Week 9 to Week 21; and the time-normalized number of moderate or severe HAE attacks (per month) from Week 5 to Week 17 and from Week 9 to Week 21 will be analyzed in a similar way to the primary efficacy endpoint.

Continuous variables will be summarized by descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) by treatment group. Continuous variables will also be analyzed using analysis of covariance or analysis of variance. The least-squares means, standard errors, and the 2-tailed 95% confidence intervals for the treatment group and placebo group will be presented.

Categorical variables will be summarized by frequency and percentage for the treatment group and placebo group. Categorical variables will be analyzed using a Pearson's Chi-square test or Cochran-Mantel-Haenszel test.

The Part B data will be summarized using descriptive statistics.

10.6.3.3. Exploratory Efficacy Analysis

Exploratory efficacy endpoints include the number of HAE attack-free patients by Week 17 and potential exposure response analysis using relevant exposure parameters and biomarkers. All

exploratory efficacy endpoints will be analyzed using the same methods as described for the secondary efficacy endpoints.

10.6.4. Pharmacokinetic Analysis

The plasma PK of ISIS 721744 will be assessed following SC administration.
Non-compartmental PK analysis of ISIS 721744 will be carried out on each individual patient dataset.

Pharmacokinetic parameters include (but are not limited to) the following: C_{max}, t_{max}, AUC, and $t_{½}$. Other plasma PK parameters, as appropriate, may be determined or calculated at the discretion of the PK scientist.

Metabolite identification and profiling may be conducted on select plasma samples.

Plasma PK parameters will be summarized using descriptive statistics. Additional details regarding the PK analysis will be described in the SAP.

Analysis of potential exposure-response relationship between biomarkers and PK measures may also be explored.

Population PK and PK/PD analyses may be performed using PK data from this study, and/or combined with other ISIS 721744 clinical PK/PD data later in the development timeline.

11. INVESTIGATOR'S REGULATORY OBLIGATIONS

11.1. Informed Consent

The written informed consent document should be prepared in the language(s) of the potential patient population, based on an English version provided by the Sponsor or designee.

Before a patient's participation in the study, the Investigator is responsible for obtaining written informed consent from the patient after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any Study Drug (ISIS 721744 or placebo) are administered. The patient must be given sufficient time to consider whether to participate in the study.

The acquisition of informed consent and the patient's agreement or refusal to notify his/her primary care physician should be documented in the patient's medical records and the ICF should be signed and personally dated by the patient and by the person who conducted the informed consent discussion (not necessarily an Investigator). The original signed ICF should be retained in the Study Master File and in any other locations required by institutional policy, and a copy of the signed consent form should be provided to the patient.

11.2. Ethical Conduct of the Study

All applicable regulations and guidelines of current GCP as well as the demands of national drug and data protection laws and other applicable regulatory requirements must be followed.

11.3. Independent Ethics Committee/Institutional Review Board

A copy of the protocol, proposed ICF, other written patient information, and any proposed advertising material must be submitted to the IEC/IRB for written approval. A copy of the written approval of the protocol and ICF must be received by the Sponsor or designee before recruitment of patients into the study and shipment of Study Drug. A copy of the written approval of any other items/materials that must be approved by the Study Center or IEC/IRB must also be received by the Sponsor or designee before recruitment of patients into the study and shipment of Study Drug. The Investigator's Brochure must be submitted to the IEC/IRB for acknowledgement.

The Investigator must submit to and, where necessary, obtain approval from the IEC/IRB, for all subsequent protocol amendments and changes to the informed consent document. The Investigator should notify the IEC/IRB of deviations from the protocol in accordance with ICH GCP. The Investigator should also notify the IEC/IRB of SAEs occurring at the Study Center and other AE reports received from the Sponsor or designee, in accordance with local procedures.

The Investigator will be responsible for obtaining annual IEC/IRB approval/renewal throughout the duration of the study. Copies of the Investigator's reports, all IEC/IRB submissions and the IEC/IRB continuance of approval must be sent to the Sponsor or designee.

11.4. Patient Confidentiality

The Investigator must ensure that the patient's confidentiality is maintained. On the case report forms or other documents submitted to the Sponsor or designee, patients should be identified by initials (if permitted by local law) and a patient identification number only. Documents that are not for submission to the Sponsor or designee (e.g., signed ICFs) should be kept in strict confidence by the Investigator.

In compliance with federal and local regulations/ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IEC/IRB direct access to review the patient's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obligated to inform and obtain the consent of the patient to permit named representatives to have access to his/her study-related records without violating the confidentiality of the patient.

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1. Protocol Amendments

Protocol amendments must be made only with the prior approval of the Sponsor or designee. Agreement from the Investigator must be obtained for all protocol amendments and amendments to the informed consent document. The regulatory authority and IEC/IRB must be informed of all amendments and give approval for any amendments likely to affect the safety of the patients

or the conduct of the study. The Investigator **must** send a copy of the approval letter from the IEC/IRB to the Sponsor or designee.

12.2. Study Termination

The Sponsor or designee reserves the right to terminate the study. The Investigator reserves the right to terminate their participation in the study, according to the terms of the Study Center contract. The Investigator/Sponsor or designee should notify the IEC/IRB in writing of the study's completion or ET and send a copy of the notification to the Sponsor or designee.

12.3. Study Documentation and Storage

An eCRF utilizing an Electronic Data Capture application will be used for this study.

The Investigator should ensure that all appropriately qualified persons to whom he/she has delegated study duties are recorded on a Sponsor-approved Delegation of Site Responsibilities Form.

Source documents are original documents, data, and records from which the patient's case report form data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, imaging, and correspondence. In this study, eCRFs may not be used as source documents.

The Investigator and Study Center staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation in accordance with ICH GCP, suitable for inspection at any time by representatives from the Sponsor or designee and/or applicable regulatory authorities. Elements should include the following:

- Patient files containing completed case report forms, informed consents, and supporting copies of source documentation
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of pre-study documentation and all correspondence to and from the IEC/IRB and the Sponsor or designee
- If drug supplies are maintained at the Study Center, proof of receipt, Study Drug Product Accountability Record, Return of Study Drug Product for Destruction, final Study Drug product reconciliation, and all drug-related correspondence

In addition, all original source documents supporting entries in the case report forms must be maintained and be readily available.

No study document should be destroyed without prior written agreement between the Sponsor or designee and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, he/she must notify the Sponsor or designee.

12.4. Study Monitoring

The Sponsor representative and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting

the various records of the study (e.g., case report forms and other pertinent data) provided that patient confidentiality is respected.

The Sponsor monitor or designee is responsible for inspecting the case report forms at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to patient medical records and other study-related records needed to verify the entries on the case report forms.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing case report forms, are resolved.

In accordance with ICH GCP and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor's Clinical Quality Assurance Department (or designees). Inspection of Study Center facilities (e.g., pharmacy, drug storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

To ensure the quality of clinical data a clinical data management review will be performed on patient data received by the Sponsor or designee. During this review, patient data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or Study Center notifications will be sent to the Study Center for completion and return to Sponsor or designee.

The Principal Investigator will sign and date the indicated places on the case report form. These signatures will indicate that the Principal Investigator inspected or reviewed the data on the case report form, the data queries, and the Study Center notifications, and agrees with the content.

12.5. Language

Case report forms must be completed in English. Generic names and trade names are acceptable for concomitant medications. Combination medications should be recorded using their trade name.

All written information and other material to be used by patients and investigative staff must use vocabulary and language that are clearly understood.

12.6. Compensation for Injury

The Sponsor maintains appropriate insurance coverage for clinical studies and will follow applicable local compensation laws. Patients will be treated and/or compensated for any study-related illness/injury in accordance with the information provided in the Compensation for Injury section of the ICF.

13. REFERENCES

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14. APPENDICES

APPENDIX A. SCHEDULE OF PROCEDURES

Appendix A Schedule of Procedures

Study Week/Day	Screening[1]	Treatment Period (12 Weeks)					Post-Treatment Period (13 Weeks)		
	Weeks -8 to -1 Days -56 to -1	Week 1 Day 1	Week 3 Day 15	Week 5 Day 29	Week 9 Day 57	Week 13 Day 85	Week 17 Day 113 or ET	Week 21 Day 141	Week 26 Day 176
Visit Window (Days)	**± 0**	**± 0**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 3**
Informed Consent	X								
Inclusion/Exclusion	X								
Demographics and Medical History (including detailed HAE history)	X								
Prior/Concomitant Medications (including HAE treatment)	X	X	X	X	X	X	X	X	X
Body Weight and Height[2]	X	X	X	X	X	X	X	X	X
Physical Examination	X	X	X	X	X	X	X	X	X
Vital Signs[3]	X	X	X	X	X	X	X	X	X
HIV, Hepatitis B, and Hepatitis C	X								
FSH[4]	X								
Pregnancy Test[5]	X	X	X	X	X	X	X	X	X
Clinical Laboratory Parameters (fasted chemistry,[6] hematology, and coagulation)[7,8]	X	X	X	X	X	X	X	X	X

Appendix A Schedule of Procedures Continued

Study Week/Day	Screening[1]	Treatment Period (12 Weeks)					Post-Treatment Period (13 Weeks)		
	Weeks -8 to -1 Days -56 to -1	Week 1 Day 1	Week 3 Day 15	Week 5 Day 29	Week 9 Day 57	Week 13 Day 85	Week 17 Day 113 or ET	Week 21 Day 141	Week 26 Day 176
Visit Window (Days)	**± 0**	**± 0**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 3**
Urinalysis	X	X	X	X	X	X	X	X	X
Threshold-Stimulated Kallikrein Activity (if applicable)[9]	X								
Genetic Diagnostic Testing (if applicable)[10]	X								
AE-QoL	X	X			X		X		X
Angioedema Activity Score[11]	X	X	X	X	X	X	X	X	X
HAE Attack Assessment (including on-demand treatment)[12,13]	X	X	X	X	X	X	X	X	X
12-Lead ECG	X	X			X		X		X
Randomization[14]		X							
Study Drug Administration (ISIS 721744 or placebo)		X		X	X	X			
Adverse Events	X	X	X	X	X	X	X	X	X
Immunogenicity Testing		X[a]			X[a]		X		X

Appendix A Schedule of Procedures Continued

Study Week/Day	Screening[1]	Treatment Period (12 Weeks)					Post-Treatment Period (13 Weeks)		
	Weeks -8 to -1 Days -56 to -1	Week 1 Day 1	Week 3 Day 15	Week 5 Day 29	Week 9 Day 57	Week 13 Day 85	Week 17 Day 113 or ET	Week 21 Day 141	Week 26 Day 176
Visit Window (Days)	**± 0**	**± 0**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 3**
PK Blood Sampling[15]		X[b]	X	X[a]	X[a]	X[b]	X	X	X
PD Blood Sampling[16]	X	X[a]	X	X[a]	X[a]	X[a]	X	X	X
Inflammatory Panel	X	X[a]	X	X[a]	X[a]	X[a]	X	X	X

Note: When multiple procedures are scheduled at the same visit, clinical assessments and procedures should be performed prior to Study Drug administration, unless otherwise indicated, and should proceed in the following order: vital signs, physical examinations, patient-reported outcomes (such as the AAS and the AE-QoL questionnaire), ECGs, and collection of blood and/or urine for laboratory assessments.

[1] The Screening Period is up to 8 weeks in duration. A patient may be randomized after fewer than 8 weeks of Screening if the patient experiences > 2 HAE attacks in less than 8 weeks and has completed all other screening activities and has met all other eligibility requirements.

[2] Height will be measured at Screening only.

[3] Vital signs will include blood pressure, heart rate, respiratory rate, and body temperature.

[4] Only for women who are not surgically sterile.

[5] Only for women who are not surgically sterile or post-menopausal. A serum pregnancy test will be performed during Screening and urine pregnancy tests will be performed at all other study visits.

[6] Fasted chemistry samples should be taken after fasting for at least 8 hours. During this time, the patient can drink water and should ensure they consume sufficient water in order to avoid dehydration.

[7] If the platelet value, serum creatinine, or liver enzyme tests are uninterpretable (e.g., due to clumping, hemolysis, or quantity not sufficient) or missing, a repeat blood specimen should be re-drawn as soon as possible (ideally within 7 days).

[8] For a complete list of laboratory analytes, refer to Appendix B.

[9] Will be assessed only in patients who have HAE-nC1-INH without a factor XII mutation or the plasminogen or angiopoietin-1 mutation.

[10] Will be performed only for patients who do not have HAE genetic diagnostic testing results prior to Screening.

Legend Continued

[11] The AAS questionnaire will be completed by patients on a daily basis (minimum of 4 daily assessments per week) for the duration of the study. Patients will be instructed on the use of the AAS during Screening and will record their HAE attacks using the AAS throughout the Screening Period (daily during up to 8 consecutive weeks) to confirm study eligibility; patients are required to experience at least 2 HAE attacks (assessed by the AAS and confirmed by the Investigator) during the Screening Period to be eligible for enrollment. If a patient experiences a third attack, the patient should be randomized as soon as possible, assuming all other screening activities have been completed and the patient meets all other eligibility requirements; in such cases, the Screening Period may be shorter than 8 weeks. Enrolled patients will continue to record HAE attacks using the AAS throughout the Treatment and Post-Treatment Periods.

[12] Historical HAE attack information will be collected at Screening. During the study, patients will be instructed to report details of any HAE attack to the study site within 72 hours of the onset of the attack. Throughout the Screening, Treatment, and Post-Treatment Periods, site personnel will contact the patient once a week (at approximately 7 days after the last contact with the patient) in order to solicit for any attack that may have occurred. In addition, during study visits, site personnel will solicit for any new HAE attack information that was not provided through patient contact with the site.

[13] The following details relating to the localization, severity, and course of all HAE attacks that occured since the previous visit will be collected: date/time of symptom onset; description of symptoms; location of symptoms (peripheral angioedema, abdominal angioedema, or laryngeal angioedema); impact of HAE attack on activity level; HAE attack severity (mild, moderate, or severe); need for assistance, medical intervention, emergency room visit, or hospitalization; medications to treat the attack; HAE attack course, including if the HAE attack(s) in question was a typical attack for the patient, or if there was an alternative diagnosis; and date/time symptoms resolved. The number of HAE attacks that required on-demand treatment, and the frequency and dose of on-demand treatment, will also be recorded.

[14] After all screening assessments have been completed and the Investigator has verified that the patient is eligible.

[15] Refer to Appendix C for the PK Sampling Schedule.

[16] To be collected fasting at each visit to assess plasma PKK, plasma proenzyme activation, and cHK levels.

Time (time is in reference to Study Drug administration [ISIS 721744 or placebo]):

a Pre-dose.
b Pre-dose, 1, 2, 4, and 6 hours post-dose.

APPENDIX B. LIST OF LABORATORY ANALYTES

Appendix B List of Laboratory Analytes

Based on emerging data from this or future studies, additional tests not listed below may be performed on stored samples to better characterize the profile of ISIS 721744 or other similar oligonucleotides.

Chemistry Panel

- Sodium
- Potassium
- Chloride
- Bicarbonate
- Total protein
- Albumin
- Calcium
- Magnesium
- Phosphorus
- Glucose
- BUN
- Creatinine
- Cholesterol
- Uric Acid
- Total bilirubin
- Direct (conjugated) bilirubin
- Indirect (unconjugated) bilirubin
- ALT
- AST
- Alkaline phosphatase
- Creatinine kinase
- GGT

Screening Tests

- Hepatitis B surface antigen
- Hepatitis C antibody
- HIV antibody
- FSH (only women who are not surgically sterile)
- Serum βhCG (only women who are not surgically sterile or post-menopausal)

Coagulation

- aPTT (sec)
- PT (sec)
- INR
- Plasmin-antiplasmin complexes
- D-dimer

Complement

- C5a
- Bb
- C4 split products

Pharmacodynamics Panel

- Plasma PKK
- Plasma proenzyme activation
- cHK

Hematology

- Red blood cells
- Hemoglobin
- Hematocrit
- MCV, MCH, MCHC
- Platelets
- White blood cells (WBC)
- WBC Differential (% and absolute)
- Neutrophils
- Eosinophils
- Basophils
- Lymphocytes
- Monocytes

Thyroid Panel

- TSH
- Free T4
- Free T3

Pharmacokinetics[1]

- ISIS 721744 levels in plasma

Immunogenicity

- Anti-ISIS 721744 antibodies

Inflammatory

- hs-CRP

Urinalysis

- Color
- Appearance
- Specific gravity
- pH
- Protein/creatinine ratio
- Protein
- Blood
- Ketones
- Urobilinogen
- Glucose
- Bilirubin
- Leukocyte esterase
- Nitrate
- eGFR
- Microscopic examination[2]

[1] Plasma PK samples may also be used for profiling of drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, or to assess other actions of ISIS 721744 with plasma constituents.

[2] Will be performed on abnormal findings unless otherwise specified.

APPENDIX C. PHARMACOKINETIC SAMPLING SCHEDULE

Appendix C Pharmacokinetic Sampling Schedule

Pharmacokinetic Sampling Schedule

Day 1	Day 15	Day 29	Day 57	Day 85	Day 113	Day 141	Day 176
Blood: Pre-dose, 1, 2, 4, and 6 hours post-dose	Blood: Anytime	Blood: Pre-dose	Blood: Pre-dose	Blood: Pre-dose, 1, 2, 4, and 6 hours post-dose	Blood: Anytime	Blood: Anytime	Blood: Anytime

APPENDIX D. GRADING SCALE FOR ADVERSE EVENTS RELATING TO LABORATORY ABNORMALITIES

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

The following grading recommendations for adverse events relating to lab test abnormalities and adverse events at the injection site are based on the CTCAE Version 5.0, November 2017.

Adverse Event	Mild	Moderate	Severe
Hematology			
aPTT prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; bleeding
Eosinophils increased[1]	>ULN and >Baseline	-	Steroids Initiated
Fibrinogen decreased	<1.0 - 0.75 x LLN; if abnormal, <25% decrease from baseline	<0.75 - 0.5 x LLN; if abnormal, 25 - <50% decrease from baseline	<0.5 x LLN; if abnormal, ≥50% decrease from baseline
Hemoglobin decreased (Anemia)	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated
Hemoglobin increased**	Increase in >0 - 2 g/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 g/dL above ULN or above baseline if baseline is above ULN	Increase in >4 g/dL above ULN or above baseline if baseline is above ULN
INR increased	>1.2 - 1.5; >1 - 1.5 times above baseline if on anticoagulation	>1.5 - 2.5; >1.5 - 2.5 x baseline if on anticoagulation; monitoring only indicated	>2.5; >2.5 x baseline if on anticoagulation; dose adjustment indicated
Lymphocyte count decreased	<LLN - 800/mm^3; <LLN - 0.8 x 10^9/L	<800 - 500/mm^3; <0.8 - 0.5 x 10^9 /L	<500 /mm^3; <0.5 x 10^9 /L
Lymphocyte count increased	-	>4000/mm^3 - 20,000/mm^3	>20,000/mm^3
Neutrophil count decreased	<LLN - 1500/mm^3; <LLN - 1.5 x 10^9 /L	<1500 - 1000/mm^3; <1.5 - 1.0 x 10^9 /L	<1000/mm^3; <1.0 x 10^9 /L
Platelet count decreased	<LLN - 75,000/mm^3; <LLN - 75.0 x 10^9 /L	<75,000 - 50,000/mm^3; <75.0 - 50.0 x 10^9 /L	<50,000/mm^3; <50.0 x 10^9 /L
White blood cell decreased	<LLN - 3000/mm^3; <LLN - 3.0 x 10^9 /L	<3000 - 2000/mm^3; <3.0 - 2.0 x 10^9 /L	<2000/mm^3; <2.0 x 10^9 /L
Chemistry			
Acidosis	pH <normal, but >=7.3	-	pH <7.3
Alanine aminotransferase increased	>ULN - 3.0 x ULN if baseline normal 1.5 - 3.0 x baseline if baseline abnormal	>3.0 - 5.0 x ULN if baseline normal >3.0 - 5.0 x baseline if baseline abnormal	>5.0 x ULN if baseline normal >5.0 x baseline if baseline abnormal
Alkaline phosphatase increased	>ULN - 2.5 x ULN if baseline normal 2.0 - 2.5 x baseline if baseline abnormal	>2.5 - 5.0 x ULN if baseline normal >2.5 - 5.0 x baseline if baseline abnormal	>5.0 x ULN if baseline normal >5.0 x baseline if baseline was abnormal
Alkalosis	pH >normal, but ≤7.5	-	pH >7.5
Aspartate aminotransferase increased	>ULN - 3.0 x ULN if baseline normal 1.5 - 3.0 x baseline if baseline abnormal	>3.0 - 5.0 x ULN if baseline normal >3.0 - 5.0 x baseline if baseline abnormal	>5.0 x ULN if baseline normal >5.0 x baseline if baseline abnormal
Blood bilirubin increased	>ULN - 1.5 x ULN if baseline normal >1.0 - 1.5 x baseline if baseline abnormal	>1.5 - 3.0 x ULN if baseline normal >1.5 - 3.0 x baseline if baseline abnormal	>3.0 x ULN if baseline normal >3.0 x baseline if baseline abnormal
Cardiac troponin I increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer

Adverse Event	Mild	Moderate	Severe
Cardiac troponin T increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer
CD4 lymphocytes decreased	<LLN - 500/mm^3; <LLN - 0.5 x 10^9 /L	<500 - 200/mm^3; <0.5 - 0.2 x 10^9 /L	<200/mm^3; <0.2 x 10^9 /L
CPK increased*	>ULN - <6 ULN	6 - 10 x ULN	>10 x ULN
Creatinine increased**	>ULN - 1.5 x ULN if baseline normal > 1.0 - 1.5 x baseline if baseline abnormal	>1.5 - 3.0 x ULN if baseline normal >1.5 - 3.0 x baseline if baseline abnormal	>3.0 x ULN if baseline normal >3.0 x baseline if baseline abnormal
GGT increased	>ULN - 2.5 x ULN if baseline normal 2.0 - 2.5 x baseline if baseline abnormal	>2.5 - 5.0 x ULN if baseline normal >2.5 - 5.0 x baseline if baseline abnormal	>5.0 x ULN if baseline normal >5.0 x baseline if baseline abnormal
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 mg/dL; >3.1 mmol/L; Ionized calcium >1.6 mmol/L; hospitalization indicated
Hyperglycemia††	Fasting glucose value ≥126 mg/dL (7.0 mmol/L)	Change in daily management to maintain fasting blood glucose <126 mg/dL (7.0 mmol/L); e.g. addition of oral antiglycemic agent; workup for diabetes	Insulin therapy initiated; hospitalization indicated
Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L; intervention initiated	>6.0; hospitalization indicated
Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 mg/dL; >1.23 mmol/L
Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L; intervention initiated	>155 mmol/L; hospitalization indicated
Hyperphosphatemia	Laboratory finding only and intervention not indicated	Noninvasive intervention indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated
Hyperuricemia	>ULN without physiologic consequences	-	>ULN with physiologic consequences
Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 mg/dL; <1.75 mmol/L; Ionized calcium <0.9 mmol/L; hospitalization indicated
Hypoglycemia‡	≥54 mg/dL - <70 mg/dL ≥3.0 mmol/L - <3.9 mmol/L	<54 mg/dL (3.0 mmol/L) AND no assistance required to actively administer carbohydrates, glucagon, or take other corrective actions	Requires assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions
Hypokalemia	<LLN - 3.0 mmol/L	symptomatic with <LLN - 3.0 mmol/L; intervention indicated	<3.0 mmol/L; hospitalization indicated
Hypomagnesemia	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 mg/dL; <0.4 mmol/L
Hyponatremia	<LLN - 130 mmol/L	125-129 mmol/L and asymptomatic	125-129 mmol/L symptomatic; 120-124 mmol/L regardless of symptoms
Hypophosphatemia	Laboratory finding only and intervention not indicated	Oral replacement therapy indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated
Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; >2.0 - 5.0 x ULN and asymptomatic	>2.0 x ULN with signs or symptoms
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; >2.0 - 5.0 x ULN and asymptomatic	>2.0 x ULN with signs or symptoms

Adverse Event	Mild	Moderate	Severe
Urine			
Proteinuria Adults Children	1+ proteinuria; urinary protein ≥ULN - <1.0 g/24 hrs -	2+ and 3+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs; Urine P/C (Protein/Creatinine) ratio 0.5 - 1.9	4+ proteinuria; Urinary protein ≥3.5 g/24 hrs; Urine P/C >1.9
Hematuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective invasive intervention indicated
Adverse Events at the Injection Site			
Adverse events at the injection site**	An event at the injection site (e.g. erythema, tenderness, itching) that is easily tolerated by the subject and does not affect the subject's usual daily activities	- Persistent (>24 hours) pain, phlebitis or edema; OR - Lipodystrophy, hair growth or alopecia, OR - Prolonged (>1 month) hypo/hyperpigmentation	- Ulceration or necrosis; severe tissue damage; operative intervention indicated, OR - Any event at the injection site that is incapacitating

†Grading for this parameter is derived from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, Sept 2007

*Grading for this parameter is derived from the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.0, Nov 2014

††Modified for consistency with ADA "Standards of Medical Care in Diabetes - 2018" Diabetes Care 2018;41(Suppl. 1):S13–S27. https://doi.org/10.2337/dc18-S002

‡Modified for consistency with ADA "Glycemic Targets: Standards of Medical Care in Diabetes - 2018", Diabetes Care 2018;41(Suppl. 1):S55–S64. https://doi.org/10.2337/dc18-S006

**Adapted from the original CTCAE V5.0 scale

IONIS PHARMACEUTICALS, INC.

ISIS 721744-CS2

A Randomized, Double-Blind, Placebo-Controlled, Phase 2a Study to Assess the Clinical Efficacy of ISIS 721744, a Second-Generation Ligand-Conjugated Antisense Inhibitor of Prekallikrein, in Patients with Hereditary Angioedema

Protocol Amendment 3 – 5 May 2020

EudraCT No: 2019-001044-22

Trial Sponsor:

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ISIS 721744-CS2

Protocol Amendment 3

EudraCT No: 2019-001044-22

Clinical Phase: 2a

A Randomized, Double-Blind, Placebo-Controlled, Phase 2a Study to Assess the Clinical Efficacy of ISIS 721744, a Second-Generation Ligand-Conjugated Antisense Inhibitor of Prekallikrein, in Patients with Hereditary Angioedema

Protocol History:

Original Protocol:	3 May 2019
Amendment 1:	21 October 2019
Amendment 2:	29 January 2020

Sponsor:
Ionis Pharmaceuticals, Inc.
Carlsbad, CA 92010

See electronic signature and date attached at end of document

PPD
Vice President and Head of Clinical Development

Confidentiality Statement

Protocol Signature Page

Protocol Number:	ISIS 721744-CS2
Protocol Title:	A Randomized, Double-Blind, Placebo-Controlled, Phase 2a Study to Assess the Clinical Efficacy of ISIS 721744, a Second-Generation Ligand-Conjugated Antisense Inhibitor of Prekallikrein, in Patients with Hereditary Angioedema
Amendment:	Amendment 3
Date:	5 May 2020

I hereby acknowledge that I have read and understand the attached clinical protocol, entitled "A Randomized, Double-Blind, Placebo-Controlled, Phase 2a Study to Assess the Clinical Efficacy of ISIS 721744, a Second-Generation Ligand-Conjugated Antisense Inhibitor of Prekallikrein, in Patients with Hereditary Angioedema," dated 5 May 2020, and agree to conduct the study as described herein.

I agree to comply with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Ionis Pharmaceuticals, Inc.

Investigator's Signature

Investigator's Name *(please print)* Date (DD Month YYYY)

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PROTOCOL AMENDMENT

Protocol Number: ISIS 721744-CS2

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 2a Study to Assess the Clinical Efficacy of ISIS 721744, a Second-Generation Ligand-Conjugated Antisense Inhibitor of Prekallikrein, in Patients with Hereditary Angioedema

Amendment Number: 3

Amendment Date: 5 May 2020

The following modifications to Protocol ISIS 721744-CS2 Amendment 2, dated 29 January 2020, have been made.

1) To adjust the length of time patients must not have received lanadelumab, prior to screening for ISIS 721744-CS2, from 6 months to 10 weeks (i.e., 5 times the ~14-day half life for lanadelumab).
2) To decrease the burden of site visits where feasible for patients, Study Drug administration, assessements and procedures may be conducted by either a Home Healthcare professional (if available) or the Study Center, as arranged by the Study Center personnel, for visits as noted in Appendix A.
3) To decrease the burden of PK sampling for patients, only a subgroup of approximately 6 patients (rather than all patients) will have blood draws of pre-dose, 1, 2, 4, and 6 hours post-dose on Day 1 and Day 85. This, along with a pre-dose and a 2 hour post-dose blood collection on Day 1 and Day 85 in all patients, will provide enough information to determine PK parameters.

Minor changes (not included in the list of changes below) have been made throughout the protocol to correct errors and/or to improve the overall clarity of the original protocol but these changes do not impact subject safety, exposure, or the overall study design.

The following table provides a summary list of major changes to the protocol:

Protocol Section	Description of Change	Rationale
PROTOCOL SYNOPSIS Study Population Exclusion Criteria Section 5.2.11.b Exclusion Criteria	Deletions in strikeout and additions in bold: 11.b Chronic prophylaxis with ~~L~~lanadelumab within **10 weeks** ~~6 months~~ prior to Screening	To adjust the length of time patients must not have received lanadelumab, prior to screening for ISIS 721744-CS2, to 5 times the ~14 day half life for lanadelumab.
PROTOCOL SYNOPSIS Study Visit Schedule and Procedures Section 6.1.2 Treatment Period	Deletions in strikeout and additions in bold: ~~The first dose of Study Drug will be administered at the Study Center on Day 1. ISIS 721744~~ **Study Drug** will be administered as a SC injection in the abdomen, thigh, or outer area of the upper arm **by qualified personnel at the Study Center or Home Healthcare professional (if available and after dosing instructions and training are provided by qualified site personnel). The first dose of Study Drug will be administered at the Study Center on Day 1.** Study ~~visits~~ **Center personnel (or Home Healthcare if available), will complete procedures~~.~~ per the Schedule of Procedures in Appendix A.** ~~will be performed during the Treatment Period at Week 1 (Administration 1), Week 3 (safety monitoring), Week 5 (Administration 2), Week 9 (Administration 3), and Week 13 (Administration 4);~~	Home healthcare provided to decrease the burden of site visits, where feasible, for patients.
Section 6.1.3 Post-Treatment Period	Additions in bold: Each patient will be followed for safety assessments for up to 13 weeks after the last dose of Study Drug. During the Post-Treatment Period, patients will return to the Study Center **(or have Home Healthcare (if available), as arranged by the Study Center personnel, per the Schedule of Procedures in Appendix A)** for visits at Weeks 17, 21, and 26/ET for safety and clinical laboratory evaluations and for blood sampling for PK/PD analyses.	Home healthcare provided to decrease the burden of site visits, where feasible, for patients.
Section 8.1 Study Drug Administration	Additions in bold: Study Drug (ISIS 721744 or placebo) will be administered as a single-SC injection once every 4 weeks by blinded study staff during on-site visits at the Study Centers **or by Home Healthcare professional (if available and after dosing instructions and training are provided by qualified site personnel)**.	Home healthcare provided to decrease the burden of site visits, where feasible, for patients.

Protocol Section	Description of Change	Rationale
Section 10.6.4 Pharmacokinetics Analysis	Deletions in strikeout and additions in bold: The plasma PK of ISIS 721744 will be assessed following SC administration. **For all patients, pre-dose (trough) and post-treatment plasma ISIS 721744 concentrations will be determined and summarized using descriptive statistics. Plasma terminal elimination half-life will also be calculated using the Post-Treatment follow up ISIS 721744 plasma concentrations, if data permits. For patients in the PK sub group, n**~~N~~on-compartmental PK analysis of ISIS 721744 will be carried out on each individual patient dataset.	Added paragraph to define how PK data will be analyzed and described
STUDY GLOSSARY Section 10.6.4 Pharmacokinetics Analysis	Additions in bold: Additional details regarding the PK analysis **along with immunogenicity (IM) analysis** will be described in the SAP.	Added "along with IM analysis" to clarify that immunogenicity analysis will be performed
Appendix A Footnote	Added: [17] Assessments and procedures may be conducted by either a Home Healthcare professional (if available), or the Study Center as arranged by the Study Center personnel. Physical Exam will be labeled Body Assessment if conducted by Home Healthcare professional. Study drug administration by Home Healthcare professional may be done only after study drug for home use is available	Home healthcare provided to decrease the burden of site visits, where feasible, for patients
Appendix A Footnote	Additions in bold: [b] Pre-dose, 1, 2, 4, and 6 hours post-dose **(PK Subgroup) or Pre-dose and 2-hours post-dose**	Added to note changes in PK schedule
Appendix A	Removed: Week 3 pregnancy test	Pregnancy test only needed every 4 weeks
Appendix B	Removed **Thyroid Panel** TSH Free T4 Free T3	Thyroid panel is not a per protocol assessment
Appendix C	Added: PK samples on Day 1 and Day 85 will be collected pre-dose, and 1, 2, 4, and 6 hours post-dose in PK subgroup only (approximately 6 patients) while pre-dose and 2 hours post-dose samples on Day 1 and Day 85 will be collected for all other patients. The rest of the sampling schedule will be the same for both sets of pateints (see table below):	Added to describe PK sampling

<table>
<tr><th>Protocol Section</th><th>Description of Change</th><th>Rationale</th></tr>
<tr><td>Appendix C</td><td>Addions in bold:
<table>
<tr><td></td><td>Day 1</td><td>Day 15</td><td>Day 29</td><td>Day 57</td><td>Day 85</td><td>Day 113</td><td>Day 141</td><td>Day 176</td></tr>
<tr><td>All Patients</td><td>Blood: Pre-dose, 2 hours post-dose</td><td>Blood Anytime</td><td>Blood: Pre-dose</td><td>Blood: Pre-dose</td><td>Blood: Pre-dose, 2 hours post-dose</td><td>Blood Anytime</td><td>Blood Anytime</td><td>Blood Anytime</td></tr>
<tr><td>PK Subgroup</td><td>Blood: Pre-dose, 1, 2, 4, and 6 hours post-dose</td><td>Blood: Anytime</td><td>Blood: Pre-dose</td><td>Blood: Pre-dose</td><td>Blood: Pre-dose, 1, 2, 4, and 6 hours post-dose</td><td>Blood: Anytime</td><td>Blood: Anytime</td><td>Blood: Anytime</td></tr>
</table></td><td>To decrease the burden of PK sampling for patients, only a subgroup of approximately 6 patients (rather than all patients) will have blood draws of pre-dose, 1, 2, 4, and 6 hours post-dose on Day 1 and Day 85.</td></tr>
</table>

PROTOCOL SYNOPSIS

Protocol Title	A Randomized, Double-Blind, Placebo-Controlled, Phase 2a Study to Assess the Clinical Efficacy of ISIS 721744, a Second-Generation Ligand-Conjugated Antisense Inhibitor of Prekallikrein, in Patients with Hereditary Angioedema
Study Phase	2a
Indication	Hereditary angioedema (HAE)
Primary Objective	The primary objective of the study is to evaluate the clinical efficacy of antisense inhibitor of prekallikrein (ISIS 721744) in patients with HAE type 1 (HAE-1), HAE type 2 (HAE-2), or HAE with normal C1-inhibitor (C1-INH).
Secondary Objectives	The secondary objectives of the study are to evaluate safety and tolerability of ISIS 721744 in patients with HAE-1/HAE-2 or HAE with normal C1-INH (HAE-nC1-INH) and to evaluate the effect of ISIS 721744 on plasma prekallikrein (PKK) and other relevant biomarkers.
Exploratory Objectives	The exploratory objectives of the study are to evaluate pharmacokinetics (PK) of ISIS 721744 (as a total full-length antisense oligonucleotide (ASO), including fully conjugated, partially conjugated, and unconjugated ISIS 721744) over time and to assess potential PK/pharmacodynamic (PD) correlations on relevant biomarkers and clinical outcomes, as appropriate.
Study Design	The study will be randomized, double-blind, and placebo-controlled in Part A and will be open-label in Part B.
Number of Patients	Approximately 24 patients with HAE are planned to be enrolled in the study: approximately 18 patients with HAE-1/HAE-2 are planned to be enrolled in Part A of the study, and, in parallel, approximately 6 patients with HAE-nC1-INH are planned to be enrolled in Part B of the study. Due to the rarity of HAE-nC1-INH, enrollment in Part B may be ended early if Study Centers are unable to enroll sufficient patients with HAE-nC1-INH; this will not impact completion of Part A.

PROTOCOL SYNOPSIS CONTINUED

Study Population	**Inclusion Criteria** 1. Patients must provide written informed consent (signed and dated) and any authorizations required by local law and be able to comply with all study requirements for the duration of the study. 2. Patients must be aged ≥ 18 years at the time of informed consent. 3. Patients must have a documented diagnosis of HAE-1/HAE-2 (for inclusion in Part A) or HAE-nC1-INH (for inclusion in Part B) as defined below: a. Documented diagnosis of HAE-1/HAE-2 based upon ALL of the following: i. Documented clinical history consistent with HAE (subcutaneous [SC] or mucosal, non-pruritic swelling episodes without accompanying urticaria) (Maurer et al. 2018). ii. Diagnostic testing results that confirm HAE-1/HAE-2: C1-INH functional level < 40% normal level. Patients with a functional level of 40% to 50% of normal can be enrolled if their complement factor C4 (C4) level is below the lower limit of normal (LLN) or if a known pathogenic mutation in the *SERPING1* gene has been demonstrated. iii. At least 1 of the following: age at reported HAE onset ≤ 30 years; a family history consistent with HAE-1/HAE-2; or complement component 1q within the normal range. b. Documented diagnosis of HAE-nC1-INH based upon documented clinical history consistent with HAE (SC or mucosal, non-pruritic swelling episodes without accompanying urticaria) (Maurer et al. 2018) AND any 1 of the following: i. A clinical diagnosis of bradykinin (BK)-mediated angioedema as confirmed with threshold-stimulated kallikrein activity and Investigator-confirmed response to acute use of a BK targeted treatment (icatibant or ecallantide-). ii. One (1) of the established mutations (c.1032C>A, Thr309Lys; c.1032C>G, Thr309Arg; c.971_1018+24del72*; or c.892_909dup) in the factor XII gene. iii. The established mutation in the plasminogen gene (c.988A>G, p.Lys330Glu). iv. The established mutation in the angiopoietin-1 gene (c.355G>T, p.A119S).

PROTOCOL SYNOPSIS CONTINUED

Study Population Continued	**Inclusion Criteria Continued** 4. Patients must: a. Experience a minimum of 2 HAE attacks (assessed by the Angioedema Activity Score [AAS] and confirmed by the Investigator) during the Screening Period. b. Complete the AAS questionnaire on a daily basis (minimum of 4 daily assessments per week) for the duration of the Screening Period. 5. Patients must have access to, and the ability to use, ≥ 1 acute medication(s) (e.g., plasma-derived or recombinant C1-INH concentrate or a BK2-receptor antagonist) to treat angioedema attacks. 6. Female patients must be non-pregnant (and not planning a pregnancy during the study) and non-lactating, and be either: a. Surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, or bilateral oophorectomy). b. Post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years of age, 12 months of spontaneous amenorrhea without an alternative medical cause and follicle-stimulating hormone [FSH] levels in the post-menopausal range for the laboratory involved). c. Abstinent (only acceptable as true abstinence, i.e., when in line with the preferred and usual lifestyle of the patient; periodic abstinence [e.g., calendar, ovulation, symptothermal, or post-ovulation methods], declaration of abstinence for the duration of the study, or withdrawal are not acceptable methods of contraception). d. If engaged in sexual relations of childbearing potential, agree to use highly effective contraceptive methods (refer to Section 6.3.1) from the time of signing the informed consent form (ICF) until at least 24 weeks after the last dose of Study Drug (ISIS 721744 or placebo). 7. Male patients must be surgically sterile or, if engaged in sexual relations with a female of childbearing potential, the patient must agree to use a highly effective contraceptive method (refer to Section 6.3.1) from the time of signing the ICF until at least 24 weeks after the last dose of Study Drug (ISIS 721744 or placebo). **Exclusion Criteria** 1. Anticipated use of short-term prophylaxis for angioedema attacks for a pre-planned procedure during the Screening or Study Periods. 2. Concurrent diagnosis of any other type of recurrent angioedema, including acquired or idiopathic angioedema. 3. Anticipated change in the use of concurrent androgen prophylaxis used to treat angioedema attacks.

PROTOCOL SYNOPSIS CONTINUED

Study Population Continued	**Exclusion Criteria Continued** 4. Any clinically significant abnormalities in screening laboratory values that would render a patient unsuitable for inclusion in the study. The following values are exclusionary: a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.5 × upper limit of normal (ULN). b. Bilirubin > 1.5 × ULN unless due to Gilbert's syndrome. c. Platelet count < LLN d. Estimated glomerular filtration rate (eGFR) < 60 mL/min (as determined by the Cockcroft Gault- Equation for creatinine clearance) e. aPTT > 1.5 × ULN 5. Patients with a history of acquired coagulopathies or bleeding diathesis (e.g., thrombocytopenia, disseminated intravascular coagulation, coagulopathy of liver disease, drug-induced platelet dysfunction, hyperfibrinolysis, acquired clotting factor inhibitors) and inherited bleeding disorders (e.g., hemophilia A, hemophilia B, other clotting factor deficiencies, qualitative platelet disorders, inherited thrombocytopenia, vascular abnormalities). 6. Any clinically significant renal or hepatic diseases. 7. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to dosing. 8. Active infection with HIV, hepatitis C or hepatitis B diagnosed by initial serological testing and confirmed with RNA testing, or prior treatment for hepatitis C. Patients at Screening who test positive by serology, but negative by RNA may be allowed in consultation with the Sponsor Medical Monitor. 9. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix that has been successfully treated. 10. Treatment with another investigational drug or biological agent within 1 month or 5 half-lives, whichever is longer, of Screening. 11. Exposure to any of the following medications: a. Angiotensin-converting enzyme (ACE) inhibitors or any estrogen-containing medications with systemic absorption (such as oral contraceptive or hormonal replacement therapy) within 4 weeks prior to Screening. b. Chronic prophylaxis with lanadelumab within 10 weeks prior to Screening. c. Oligonucleotides (including small interfering RNA) within 4 months of Screening if single dose received, or within 12 months of Screening if multiple doses received. 12. Any condition that, in the opinion of the Investigator, may compromise the patient's safety or compliance, preclude successful conduct of the study, or interfere with the interpretation of results

PROTOCOL SYNOPSIS CONTINUED

Prohibited Concomitant Medications	The following medications/procedures will not be permitted during the study: • Chronic prophylaxis for angioedema attacks, except for a stable dose of androgens. Any use of lanadelumab will not be permitted. **NOTE:** The use of acute medications (plasma-derived or recombinant C1-INH concentrate or BK2-receptor antagonist) to treat angioedema attacks is allowed as medically indicated. • ACE inhibitors or any estrogen-containing medications with systemic absorption (such as oral contraceptive or hormonal replacement therapy). • Any oligonucleotides (including small interfering RNA) other than ISIS 721744. • Plasmapheresis. • Any other investigational drug or device.
Treatment Groups	A total of approximately 24 patients in Parts A and B combined will be administered SC injections of ISIS 721744 80 mg or placebo every 4 weeks. Patients will be allocated into Part A or Part B according to type of HAE, (i.e., either HAE-1/HAE-2 in Part A or HAE-nC1-INH in Part B) as follows: • In Part A, approximately 18 patients with HAE-1/HAE-2 will be randomized to SC injections of ISIS 721744 80 mg or placebo in a 2:1 ratio (ISIS 721744:placebo). • In Part B, approximately 6 patients with HAE-nC1-INH will be administered open-label SC injections of ISIS 721744 80 mg. Due to the rarity of HAE-nC1-INH, enrollment in Part B may be ended early if Study Centers are unable to enroll sufficient patients; this will not impact the completion of Part A.
Study Drug Dosage and Administration	The Study Drug (ISIS 721744 or placebo) is contained in 2-mL stoppered glass vials. The Study Drug (ISIS 721744 or placebo) and its storage and preparation instructions will be provided by the Sponsor or designee. The Study Drug (ISIS 721744 or placebo) must be stored securely at 2 °C to 8 °C and be protected from light. During the Treatment Period, Study Drug (ISIS 721744 or placebo) will be administered as a single SC injection every 4 weeks.

PROTOCOL SYNOPSIS CONTINUED

Rationale for Dose and Schedule Selection	The dose level of 80 mg every 28 days was selected based on the safety, tolerability, PK, and PD data from the ISIS 721744-CS1 study in healthy volunteers. The Phase 1 study evaluated doses of 20, 40, 60, and 80 mg ISIS 721744 administered once every 4 weeks for a total of 12 weeks. All dose levels were generally well-tolerated and induced a dose and exposure-dependent reduction in plasma PKK, a biomarker for BK and vascular permeability. The highest dose level of 80 mg produced near-complete reduction of plasma PKK levels (a mean reduction of 93.6% from Baseline on Day 99 [2 weeks after the last dose]). The estimated half-life ($t_{½}$) from the Phase 1 PK data was approximately 4 to 5 weeks, supporting the once-every-28-day dosing regimen. Pharmacokinetic/PD analysis of the Phase 1 data suggested very minor differences in plasma PKK reductions at doses higher than 80 mg.
Adjustment of Dose and/or Treatment Schedule	Down-titration of Study Drug (ISIS 721744 or placebo) will not be allowed during the study. Action taken with Study Drug (ISIS 721744 or placebo) due to an adverse event (AE) is characterized by 1 of the following: • None: No changes made to Study Drug (ISIS 721744 or placebo) administration and dose. • Not Applicable: AE reported during the Screening Period prior to Study Drug (ISIS 721744 or placebo) administration. • Permanently Discontinued: Study Drug (ISIS 721744 or placebo) discontinued and not restarted. • Temporarily Interrupted, Restarted – Same Dose: Dosing and/or dosing frequency temporarily interrupted/changed or delayed due to the AE and restarted at the same dose.
Study Visit Schedule and Procedures	The study will be conducted concurrently in 2 parts (Part A and Part B); patients will be allocated into Part A or Part B according to type of HAE (i.e., either HAE-1/HAE-2 in Part A or HAE-nC1-INH in Part B). Part A is randomized, double-blind, and placebo-controlled; and Part B is open-label. The study visit schedule and procedures are nearly identical in Part A and Part B, and thus are presented together; any differences are indicated where applicable. Patients will be screened for eligibility criteria following written informed consent. During the Screening Period, the following assessments will be performed: demographics; medical history, including a detailed HAE history; prior and concomitant medications, including type of prophylaxis (if used) and type of acute treatment; HIV, hepatitis B, and hepatitis C screening; pregnancy testing for women of childbearing potential and FSH testing for confirmation of menopause per inclusion criteria; quality of life as assessed by the angioedema quality of life (AE QoL) questionnaire; attack frequency, as assessed by the AAS daily during up to 8 consecutive weeks, and confirmed by the Investigator; HAE attack assessment; physical examinations, including vital signs, body height, and weight; electrocardiograms (ECGs); AEs; PD blood sampling; inflammatory panel; and clinical laboratory assessments (chemistry, hematology, coagulation, and urinalysis).

PROTOCOL SYNOPSIS CONTINUED

Study Visit Schedule and Procedures Continued	Threshold stimulated kallikrein activity will be assessed only in patients who have HAE-nC1-INH without a factor XII mutation or the plasminogen or angiopoietin-1 mutation. Genetic testing will be performed only for patients who do not have HAE genetic diagnostic testing results prior to Screening. During the Screening Period, patients must experience a minimum of 2 HAE attacks (assessed by the AAS and confirmed by the Investigator) to be eligible for the study; patients will be instructed to report details of any HAE attack to the study site within 72 hours of the onset of the attack. Throughout the Screening Period, site personnel will contact the patient once a week (at approximately 7 days after the last contact with the patient) in order to inquire about any attack that may have occurred. If a patient experiences a third attack, the patient should be randomized as soon as possible, assuming all other screening activities have been completed and the patient meets all other eligibility requirements; in such cases, the Screening Period may be shorter than 8 weeks. During the course of the study, the use of acute medications (plasma derived or recombinant C1 INH concentrate, BK2-receptor antagonist, or kallikrein inhibitor) to treat angioedema attacks is allowed as medically indicated. Patients can be treated with on demand therapy as determined by their treating physician. After a Screening Period of up to 8 weeks, those patients who had at least 2 documented attacks (assessed by the AAS and confirmed by the Investigator) during the Screening Period will be enrolled and/or randomized to receive ISIS 721744 80 mg or placebo (Part A) or open label ISIS 721744 80 mg (Part B) every 4 weeks for a total Treatment Period of 12 weeks. Study Drug will be administered as a SC injection in the abdomen, thigh, or outer area of the upper arm by qualified personnel at the Study Center or Home Healthcare professional (if available and after dosing instructions and training are provided by qualified site personnel). The first dose of Study Drug will be administered at the Study Center on Day 1. Study Center personnel (or Home Healthcare if available), will complete procedures per the Schedule of Procedures in Appendix A. After completion of the Week 13 visit, eligible patients may elect to enroll in the Open-Label Extension (OLE) Study (ISIS 721744-CS3), pending study approval by the IRB/IEC and the appropriate regulatory authority, and will need to sign the Institutional Review Board/Independent Ethics Committee (IRB/IEC) approved informed consent. Patients who complete Study Visit Week 17, and meet eligibility requirements, may start the treatment period in the CS3 study anytime after the Week 17 visit and discontinue participation in the CS2 Post-Treatment Evaluation Period.

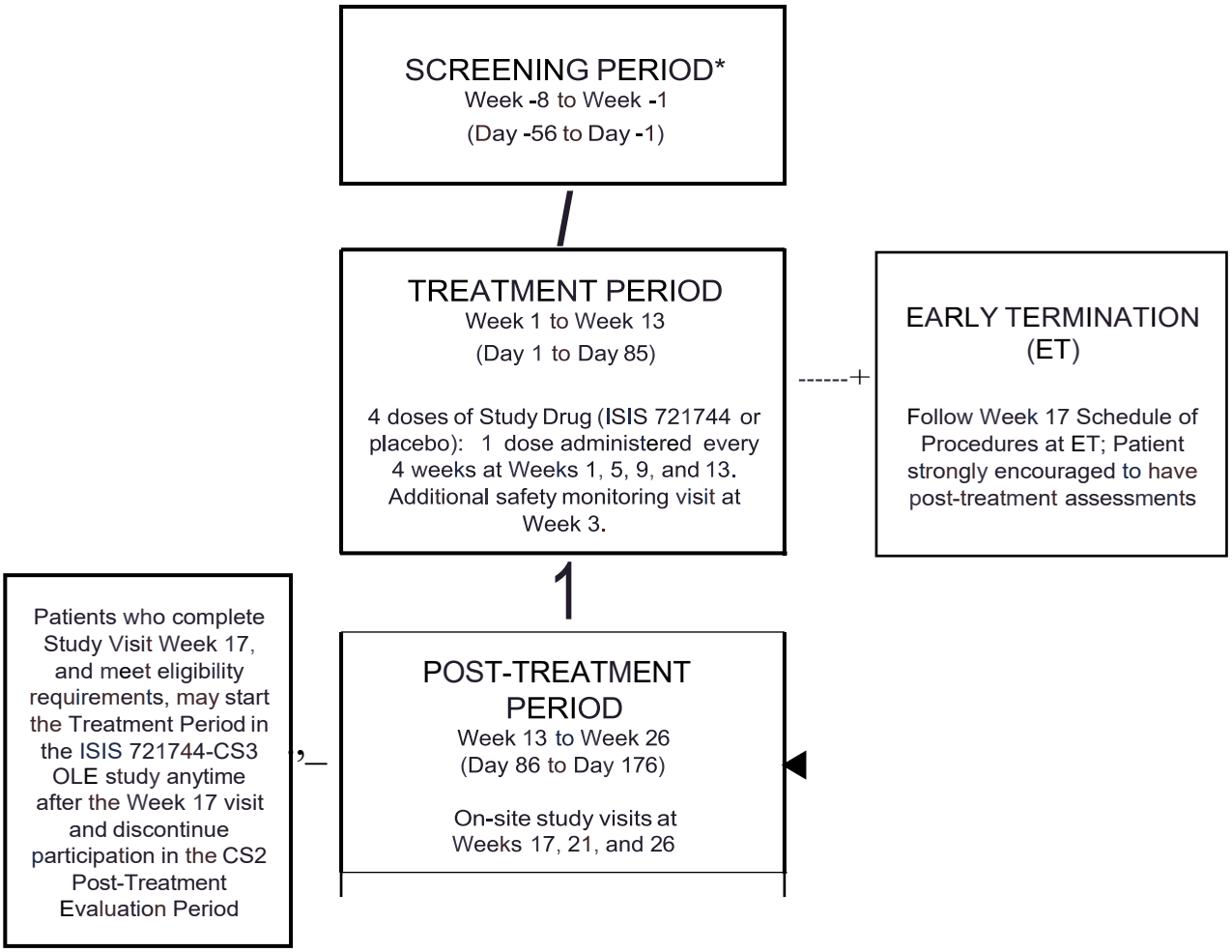
PROTOCOL SYNOPSIS CONTINUED

Study Visit Schedule and Procedures Continued	During the study, patients will be instructed to report details of any HAE attack to the study site within 72 hours of the onset of the attack. During the Treatment and Post-Treatment Periods, the following data will be collected: daily AAS and number of HAE attacks (assessed by the AAS and confirmed by the Investigator); number of HAE attacks that required on-demand treatment; HAE attack details, including localization, severity, course, and details of any required treatment (i.e., frequency and dose); and vital signs. Throughout the Treatment and Post-Treatment Periods, site personnel will contact the patient once a week (at approximately 7 days after the last contact with the patient) in order to inquire about any attack that may have occurred. In addition, at study visit time points, site personnel will inquire about any new HAE attack information that was not provided through patient contact with the site. See Section 6.2.1 for further information on the collection of data surrounding HAE attacks. Additionally, blood will be collected at every visit during the Treatment and Post-Treatment Periods to assess PD and coagulation parameters, including, but not limited to: plasma PKK, plasma proenzyme activation, cleaved high molecular weight kininogen (cHK) levels, D-dimer levels, activated partial thromboplastin time (aPTT), plasmin-antiplasmin complexes, C4 split products, and platelet counts. Blood samples will also be collected regularly throughout the study for safety and PK/PD analyses. Additional assessments will be performed throughout the study as indicated in the Schedule of Procedures table in Appendix A. Patients who discontinue treatment will remain in the study and attend the Early Termination (ET) Visit unless consent is withdrawn. Detailed information regarding the CS2 procedures is presented in Section 6 and Appendix A. Appendix B includes a list of laboratory analytes required for the study.
Primary Endpoint	The primary endpoint is the time-normalized number of HAE attacks (per month) from Week 1 to Week 17.
Secondary Endpoints	Secondary endpoints include the following: • The time-normalized number of HAE attacks (per month) from Week 5 to Week 17 • The time-normalized number of moderate or severe HAE attacks (per month) from Week 5 to Week 17 • The number of patients with a clinical response (defined as a ≥ 50%, ≥ 70%, or ≥ 90% reduction from Baseline in HAE attack rate) by Week 17 • The number of HAE attacks requiring acute therapy from Week 5 to Week 17 • cHK levels at Weeks 9 and 17 • PKK activity at Weeks 9 and 17 • Consumption of on-demand medication at Weeks 9 and 17 • AE-QoL questionnaire score at Weeks 9 and 17

PROTOCOL SYNOPSIS CONTINUED

Exploratory Endpoints	Exploratory endpoints include the following: • The number of HAE attack-free patients by Week 17 • PK parameters, including, but not limited to: maximum observed plasma concentration (C_{max}), time to C_{max}, area under the plasma concentration-time curve, and $t_{½}$ • Potential exposure-response analysis using relevant exposure parameters and biomarkers
Safety Endpoints	The safety and tolerability of ISIS 721744 will be assessed by determining the number, type, severity, and dose-relationship of AEs; vital signs; ECGs; and clinical laboratory parameters. Safety results in patients dosed with ISIS 721744 will be compared to safety results in patients dosed with placebo.
Statistical Considerations	The sample size of 18 patients with HAE-1/HAE-2 (12 patients administered SC injections of ISIS 721744 80 mg and 6 patients administered placebo) is from clinical considerations for sufficient safety and tolerability evaluation. The primary endpoint is the time-normalized number of HAE attacks (per month) from Week 1 to Week 17. From historical data, the placebo group is estimated to have 6.8 HAE attacks per 4-month period. If the ISIS 721744 80 mg group is assumed to have 2.8 HAE attacks per 4-month period, then with a 0.05 significance level and Poisson model, the sample size of 18 patients will provide at least 90% power for the primary endpoint, considering a 10% missing data or dropout rate for both active treatment and placebo. There is no statistical rationale for the sample size of 6 patients with HAE-nC1-INH. An independent Data and Safety Monitoring Board (DSMB) will be established prior to the initiation of the study. The DSMB will be responsible for monitoring the overall safe conduct of the study. Based on its ongoing assessment of the safety and tolerability of ISIS 721744, the DSMB will provide recommendations to the Sponsor for modifying, stopping, or continuing the study as planned. Details on the safety assessments, frequency of review, meeting schedules and controlled access to unblinded data are outlined in the DSMB Charter and Statistical Analysis Plan.
Sponsor	Ionis Pharmaceuticals, Inc.

STUDY DESIGN AND TREATMENT SCHEMA



* The Screening Period is up to 8 weeks in duration. A patient may be randomized after fewer than 8 weeks of Screening if the patient experiences 2 HAE attacks in less than 8 weeks and has completed all other screening activities and has met all other eligibility requirements.

STUDY GLOSSARY

Abbreviation	Definition
2′-MOE	2′-*O*-(2-methoxyethyl)
AAS	Angioedema Activity Score
ACE	angiotensin-converting enzyme
ADR	adverse drug reaction
AE(s)	adverse event(s)
AE-QoL	angioedema quality of life
AESI	adverse event of special interest
ALT	alanine aminotransferase
aPTT	activated partial thromboplastin time
ASO	antisense oligonucleotide
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
Bb	complement factor Bb (activated complement split product)
βhCG	beta-subunit of human chorionic gonadotropin (pregnancy test)
BK	bradykinin
BUN	blood urea nitrogen
C	centigrade
C1-INH	C1-inhibitor
C4	complement factor C4
C5a	complement factor C5a (activated complement split product)
cHK	cleaved high molecular weight kininogen
C_{max}	maximum observed plasma concentration
CTCAE	Common Terminology Criteria for Adverse Events
dL	deciliter
DNA	deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
ECG	electrocardiogram
eCRF	electronic Case Report Form
eGFR	estimated glomerular filtration rate
ET	Early Termination
FSH	follicle-stimulating hormone
$GalNAc_3$	*N*-acetyl galactosamine
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HAE	hereditary angioedema
HAE-1	hereditary angioedema type 1
HAE-2	hereditary angioedema type 2
HAE-nC1-INH	hereditary angioedema with normal C1-inhibitor
HIV	human immunodeficiency virus
HK	high molecular weight kininogen
hs-CRP	C-reactive protein measured by high sensitivity assay
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee

IgM	immunoglobulin M
IM	imunogenicity
INR	international normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISIS 721744	antisense inhibitor of prekallikrein
ITT	Intent-to-Treat
LCRIS	local cutaneous reaction at injection site
LLN	lower limit of normal
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA™	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid
NCS	not clinically significant
OLE	open-label extension
PD	pharmacodynamic(s)
pH	measure of the acidity or basicity of a solution
PK	pharmacokinetic(s)
PKa	plasma kallikrein
PKK	prekallikrein
PP	Per-Protocol
PT	prothrombin time
RNA	ribonucleic acid
RNase H1	an ubiquitous endonuclease that specifically hydrolyzes the RNA strand in RNA/DNA hybrids
SAE	serious adverse event
SAP	Statistical Analysis Plan
SC	subcutaneous(ly)
Study Day 1	defined as the first day Study Drug is administered to the patient
Study Drug	ISIS 721744 or placebo
SUSAR	suspected unexpected serious adverse reaction
$t_{½}$	half-life
T3	triiodothyronine
T4	thyroxine
TEAE	treatment-emergent adverse event
T_{max}	time to maximum observed plasma concentration
TSH	thyroid-stimulating hormone
ULN	upper limit of normal
WBC	white blood cell
WOCBP	woman/women of childbearing potential

1. OBJECTIVES AND ENDPOINTS

1.1. Objectives

1.1.1. Primary Objective

The primary objective of the study is to evaluate the clinical efficacy of antisense inhibitor of prekallikrein (ISIS 721744) in patients with hereditary angioedema (HAE) type 1 (HAE-1), HAE type 2 (HAE-2), or HAE with normal C1-inhibitor (C1-INH).

1.1.2. Secondary Objectives

The secondary objectives of the study are to evaluate safety and tolerability of ISIS 721744 in patients with HAE-1/HAE-2 or HAE with normal C1-INH (HAE-nC1-INH) and to evaluate the effect of ISIS 721744 on plasma prekallikrein (PKK) and other relevant biomarkers.

1.1.3. Exploratory Objectives

The exploratory objectives of the study are to evaluate pharmacokinetics (PK) of ISIS 721744 (as a total full-length antisense oligonucleotide [ASO], including fully conjugated, partially conjugated, and unconjugated ISIS 721744) over time and to assess potential PK/pharmacodynamic (PD) correlations on relevant biomarkers and clinical outcomes, as appropriate.

1.2. Study Endpoints

The definition of an HAE attack, including discrete attacks, is provided in Section 6.2.1.

1.2.1. Primary Endpoints

The primary endpoint is the time-normalized number of HAE attacks (per month) from Week 1 to Week 17.

1.2.2. Secondary Endpoints

Secondary endpoints include the following:

- The time-normalized number of HAE attacks (per month) from Week 5 to Week 17
- The time-normalized number of moderate or severe HAE attacks (per month) from Week 5 to Week 17
- The number of patients with a clinical response (defined as a ≥ 50%, ≥ 70%, or ≥ 90% reduction from Baseline in HAE attack rate) by Week 17
- The number of HAE attacks requiring acute therapy from Week 5 to Week 17
- Cleaved high molecular weight kininogen (cHK) levels at Weeks 9 and 17
- PKK activity at Weeks 9 and 17
- Consumption of on-demand medication at Weeks 9 and 17
- Angioedema quality of life (AE-QoL) questionnaire score at Weeks 9 and 17

1.2.3. Safety Endpoints

The safety and tolerability of ISIS 721744 will be assessed by determining the number, type, severity, and dose-relationship of adverse events (AEs); vital signs; electrocardiograms (ECGs); and clinical laboratory parameters. Safety results in patients dosed with ISIS 721744 will be compared to safety results in patients dosed with placebo.

1.2.4. Exploratory Endpoints

Exploratory endpoints include the following:

- The number of HAE attack-free patients by Week 17
- PK parameters, including, but not limited to: maximum observed plasma concentration (C_{max}), time to C_{max} (T_{max}), area under the plasma concentration-time curve (AUC), and half-life ($t_{½}$)
- Potential exposure response analysis using relevant exposure parameters and biomarkers

2. BACKGROUND AND RATIONALE

2.1. Overview of Disease

Hereditary angioedema is a rare genetic disorder that is characterized by disabling recurrent episodes of local skin swellings, painful abdominal attacks, and, occasionally, laryngeal attacks that can be life-threatening. The disorder is classified in 3 subtypes. Hereditary angioedema Type I (HAE-1) and Type II (HAE-2) are caused by an autosomal dominant mutation in the *SERPING1* gene, resulting in either decreased levels of C1-INH (HAE-1) or loss-of-function of this protein (HAE-2) (Bissler et al. 1997). The third form of HAE is associated with normal levels and function of C1-INH (HAE-nC1-INH). This form is currently categorized as 4 subtypes, with either specific genetic mutations in the factor XII gene, the plasminogen gene, or the angiopoietin-1 gene, or due to an unknown cause (Maurer et al. 2018). Extensive evidence from *in vitro* and *in vivo* studies supports the key role of bradykinin (BK) in HAE attacks, although the data linking HAE-nC1-INH with BK are less strong (Zuraw and Christiansen 2016). Diagnosing HAE-nC1-INH can be challenging given the large heterogeneity of this patient population, the lack of diagnostic tests, and the fact that specific genetic mutations account only partially for the occurrence of this type of HAE. Recently, a threshold-stimulated kallikrein activity assay was shown to discriminate BK-mediated angioedema from histamine-mediated angioedema (Lara-Marquez et al. 2018). This technique may, therefore, enhance the identification of HAE-nC1-INH patients that are likely to benefit from inhibition of the contact activation pathway.

Treatment options for HAE include on-demand treatment of attacks and prophylaxis. On-demand options include supplementation of C1-INH (either plasma-derived or recombinant C1-INH concentrate) and inhibition of BK2 receptor activation (BK2-receptor antagonist). In addition, tranexamic acid may relieve symptoms in non-severe angioedema attacks. Prophylactic regimens for HAE include plasma-derived C1-INH concentrate (administered either

intravenously or subcutaneously [SC]), attenuated androgens, antifibrinolytics and a recently Food and Drug Administration-approved monoclonal antibody directed against plasma kallikrein (PKa). Kallikrein circulates in plasma as a zymogen (i.e., PKK) which is bound to one of its main substrates, high molecular weight kininogen (HK). Prekallikrein is cleaved upon contact activation, forming the active protease PKa. Plasma kallikrein cleaves HK in turn, thereby releasing BK and the split product cHK. The binding of BK to the BK2 receptor leads to activation of various intracellular signaling pathways resulting in vasodilation, chemotaxis of neutrophils, and increased vascular permeability and fluid efflux, which typically characterize an angioedema attack (Zuraw and Christiansen 2016).

2.2. Therapeutic Rationale

ISIS 721744 is a second-generation, ligand-conjugated antisense oligonucleotide (ASO) drug designed to reduce the production of PKK mRNA. Antisense technology is characterized by its high specificity in inhibiting a single-gene product, thereby diminishing the potential for off-target drug effects. Furthermore, since ligand-conjugated ASOs require infrequent administration, ~once every month or even less often, the availability of a plasma PKK inhibitor could be of additional value to the arsenal of prophylactic drugs for the prevention of HAE attacks. The long $t_{½}$ of second-generation antisense drugs and the lower frequency of administration afforded by ligand conjugation might provide additional benefit to patients.

The Phase 1 clinical data show that ISIS 721744 inhibits plasma PKK effectively in a dose-dependent manner without safety concerns.

2.3. ISIS 721744

2.3.1. Mechanism of Action

ISIS 721744 is an *N*-acetyl galactosamine ($GalNAc_3$)-conjugated, second-generation ASO drug targeted to human PKK. It is complementary to the translated regions (Exon 9) of the PKK protein messenger ribonucleic acid (mRNA) and, following cleavage of the $GalNAc_3$ moiety, binds to the mRNA by Watson and Crick base pairing. The hybridization (binding) of ISIS 721744 to the cognate mRNA results in the ubiquitous endonuclease that specifically hydrolyzes the RNA strand in RNA/DNA hybrids (RNase H1)-mediated degradation of the PKK mRNA, thus preventing production of the PKK protein. Maximal antisense-mediated reduction of target mRNA levels is typically greater than 90% of control levels in sensitive tissues (Crooke and Bennett 1996; Zhang et al. 2010). Furthermore, reduction in target mRNA levels using this approach correlates directly with a subsequent reduction in target protein levels.

2.3.2. Chemistry

Chemically, ISIS 721744 is a synthetic oligomer of 20 nucleotides (i.e., a 20-mer) that are connected sequentially by phosphorothioate and phosphodiester linkages (mixed backbone design). The nucleotide sequence of ISIS 721744 (Figure 1) is complementary to a 20-nucleotide stretch within Exon 9 of the PKK protein mRNA. Structurally, the oligonucleotide has 4 regions. Two (2) of them, the 5 nucleotides at the 5′ end and the 5 nucleotides at the 3′ end, are composed of 2′-*O*-(2-methoxyethyl) (2′-MOE)-modified ribonucleotides. These 2′-MOE-modified nucleotides confer (1) increased affinity to the target

mRNA (Altmann et al. 1996; McKay et al. 1999), (2) increased resistance to exonucleases and endonucleases (thereby increasing stability in tissue) (Geary et al. 2003), and (3) amelioration of some of the high-dose toxicities thereby resulting in an improved safety profile compared to first-generation antisense drugs containing phosphorothioate modified oligodeoxynucleotides (Henry et al. 2000). The third region, the central portion of the oligonucleotide, is composed of 10 oligodeoxynucleotides. This chimeric design is called a MOE-Gapmer, and ISIS 721744 employs this chimeric structure to enable use of the RNase H1-mechanism for antisense activity. This is because while the 2′-MOE modification confers increased stability and affinity, it does not support RNase H1-catalyzed cleavage of ribonucleic acid (RNA) hybridized to 2′-MOE-modified nucleotides (McKay et al. 1999). This is caused by conformational changes induced in the heteroduplex by 2′-alkoxy:RNA hybrids that are not recognized by RNase H1 enzyme (Inoue et al. 1987; Monia et al. 1993). By limiting the 2′-MOE modification to nucleotides flanking the phosphorothioate oligodeoxynucleotide core, the beneficial attributes of the 2′-MOE chemistry are preserved while also retaining RNase H1 recognition. A fourth region, comprised of a triantennary cluster of $GalNAc_3$ sugars, is linked to the 5′ end of ISIS 721744 via a phosphodiester linkage. The $GalNAc_3$ cluster is a high-affinity ligand for the asialoglycoprotein receptor, a receptor expressed primarily on the surface of liver hepatocytes (Stockert 1995). The $GalNAc_3$ cluster enhances delivery of ISIS 721744 to liver hepatocytes over other cell types and enhances potency. After internalization into cells, the $GalNAc_3$ cluster is metabolized to release “free ASO” inside the cell (Prakash et al. 2014). The internucleosidic linkages are a mixture of phosphorothioate and phosphodiester. The phosphorothioate linkages are introduced into the deoxyribonucleic acid (DNA) gap region and at both ends of the oligonucleotide to protect it from nuclease mediated metabolism. The mixed backbone design reduces the total number of phosphorothioate linkages, which reduces non-specific interactions with proteins and further enhances potency and therapeutic index of $GalNAc_3$-conjugated ASOs.

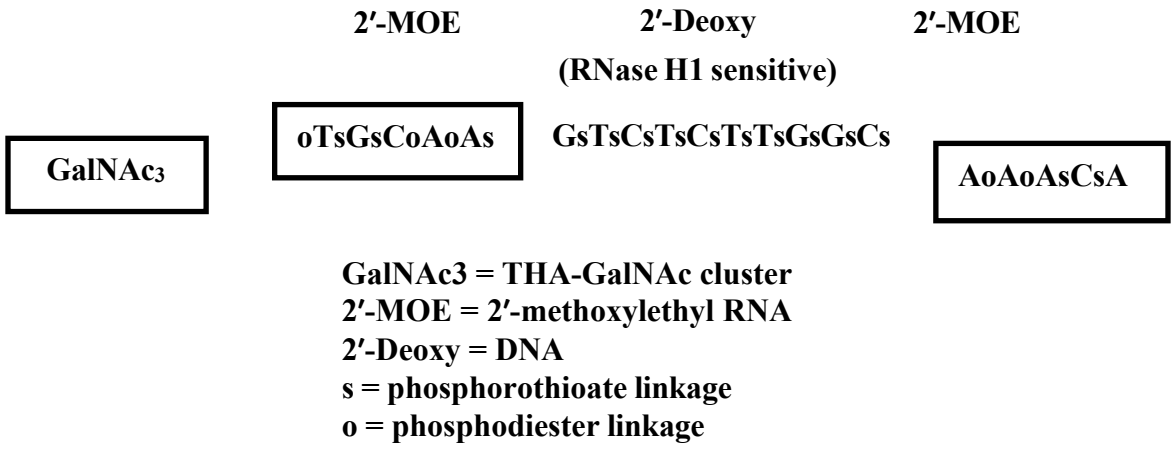


Figure 1: Design of $GalNAc_3$-Conjugated Chimeric 2′-MOE Phosphorothioate Oligonucleotides (MOE-Gapmer)

The sequence of ISIS 721744 is shown.

2.3.3. Preclinical Experience

Detailed information concerning the preclinical studies conducted with PKK ASO ISIS 546254, its 5′-GalNAc$_3$-conjugated mixed backbone variant ISIS 721744, and mouse surrogate PKK ASOs can be found in the Investigator's Brochure.

The results support the concept that inhibition of PKK through antisense mechanism may serve as a new and effective strategy for the prophylaxis of HAE. Results also strongly support that GalNAc$_3$-conjugation of PKK ASO significantly increases the potency of ASO for inhibition of PKK hepatic mRNA and circulatory protein expression and thus these ASOs should be a useful therapeutic strategy for the prophylactic treatment of HAE.

2.3.4. Clinical Experience

ISIS 721744 has been evaluated in the clinical setting in a Phase 1 safety study (ISIS 721744-CS1). All subjects have completed study procedures and final safety and PD data are available. A summary is included below. Please refer to the Investigator's Brochure for a detailed description of the preclinical pharmacology, nonclinical toxicology and PK, as well as a description of previous clinical experience with other related 2′-MOE phosphorothioate oligonucleotides.

ISIS 721744 has been studied in 32 healthy volunteers in a double-blind, multiple-dose, dose-escalation study. Of these, 24 subjects received multiple doses of ISIS 721744. The 32 subjects were randomized into 4 cohorts (6 subjects each) to receive once-every-4-week SC doses of ISIS 721744 20, 40, 60, or 80 mg, or placebo (8 subjects) for a total of 12 weeks (4 total doses). All subjects received all planned doses of Study Drug (ISIS 721744 or placebo). The duration of Study Drug exposure was 84 days for each subject.

No serious adverse events (SAEs) were reported in the ISIS 721744-CS1 study. There were no early discontinuations from Study Drug or the study, and all subjects in the ISIS 721744 and placebo arms completed all study procedures. Adverse events at the injection site (defined as any preferred term containing "injection site") were the most commonly reported treatment-emergent adverse events (TEAEs) in the ISIS 721744 treatment arms; no injection site-related TEAEs were reported in the placebo arm. There were no flu-like reactions or events of local cutaneous reaction at injection site (LCRIS) reported; LCRIS events were defined as (A) moderate or severe injection site erythema, swelling, pruritus, pain, or tenderness that started on the day of injection and persisted for at least 2 days; or (B) any AE at the injection site, regardless of severity, that led to discontinuation of Study Drug, where AE at the injection site was the principal reason for discontinuation. No relationship between incidence of TEAEs and the dose administered was observed.

Thirteen (13) AEs related to study treatment were reported for 4 (16.7%) subjects in the ISIS 721744 arm, and for 1 subject (2 events; 12.5%) in the placebo arm. One (1) subject each in the ISIS 721744 and placebo arm reported AEs of ECG T wave inversion (preferred term) that were assessed as related. Nine (9) of the total 13 related events with ISIS 721744 concerned injection site-related events and were reported by 1 subject in the 80 mg arm. Additional related events were tinnitus (1 subject, 1 event in the 60 mg arm), headache (1 subject, 1 event in the 60 mg arm), and epistaxis (1 subject, 1 event in the 20 mg arm). All TEAEs related to study treatment were mild in severity, and none were serious.

ISIS 721744 resulted in a dose-dependent reduction of PKK concentration and plasma proenzyme activation. The difference in absolute and percent change from Baseline for ISIS 721744 vs. placebo was statistically significant for PKK concentration for 40, 60, and 80 mg ($p \leq 0.043$) starting at Day 15, the first evaluation, and for 20 mg starting at Day 29, and for plasma proenzyme activation for all doses ($p \leq 0.002$) starting at Day 15. The nadir was generally reached around Day 71, when the percent reduction with the 80 mg dose was -93.2% for PKK concentration and -99.6% for plasma proenzyme activation.

The difference in absolute and percent change from Baseline in cHK for ISIS 721744 vs. placebo was not statistically significant at any visit.

Clinical data from other $GalNAc_3$-conjugated 2′-MOE-gapmer oligonucleotides suggest that enhanced delivery of ISIS 721744 to hepatocytes vs. non-parenchymal cells will result in similar PD results as ISIS 546254 at $1/10^{th}$ to $1/30^{th}$ of the dose (Viney et al. 2016).

2.4. Rationale for Dose and Schedule of Administration

The dose level of 80 mg every 28 days was selected based on the safety, tolerability, PK, and PD data from the ISIS 721744-CS1 study in healthy volunteers. The Phase 1 study evaluated doses of 20, 40, 60, and 80 mg ISIS 721744 administered once every 4 weeks for a total of 12 weeks. All dose levels were generally well-tolerated and induced a dose- and exposure-dependent reduction in plasma PKK, a biomarker for BK and vascular permeability. The highest dose level of 80 mg produced near-complete reduction of plasma PKK levels (a mean reduction of 93.6% from Baseline on Day 99 [2 weeks after the last dose]). The estimated $t_{½}$ from the Phase 1 PK data was approximately 4 to 5 weeks, supporting the once-every-28-day dosing regimen. Pharmacokinetic/PD analysis of the Phase 1 data suggested very minor differences in plasma PKK reductions at doses higher than 80 mg.

2.5. Benefit-Risk Assessment

2.5.1. Benefit Assessment

The benefits of treatment of ISIS 721744 are currently unknown. Due to its mechanism of action, ISIS 721744 has the potential to be efficacious for the treatment of patients with HAE.

2.5.2. Risk Assessment

The known potential risks to study participants associated with ISIS 721744 are elaborated on in the “Guidance to Investigator” section of the Investigator’s Brochure.

There are no anticipated risks associated with reducing plasma PKK levels; however, a potential theoretical risk associated with PKK inhibition would be prolongation of activated partial thromboplastin time (aPTT). This risk is informed by 80 cases of PKK deficiency that have been described in the literature (Girolami et al. 2010). In these individuals, there is a discrepancy between an observed *in vitro* defect and an absence of bleeding. Thus, it is believed that most cases go undetected or, if detected, go unreported. Occasional bleeding or thrombosis has been reported in a few PKK deficient patients but these instances were due to the presence of associated risk factors. Diagnosis is based on the prolongation of partial thromboplastin time and normal prothrombin time (PT) and thrombin time. In these individuals, platelet and vascular

tests are normal and the long partial thromboplastin time has shown to be fully corrected by the addition of normal plasma or normal serum.

In monkeys, doses of ISIS 721744 of up to 30 mg/kg/wk for 13 weeks were well-tolerated with the exception of thrombocytopenia observed in 1 female at 12 mg/kg/wk and 1 male at 30 mg/kg/wk. The monkey dose of 6 mg/kg/wk provides an approximate 20-fold margin relative to a human dose of 80 mg every 4 weeks and therefore there is sufficient therapeutic margin to assure the safe clinical use of ISIS 721744 at the proposed clinical dose and regimen.

One (1) subject in the ISIS 721744-CS1 study had a confirmed platelet nadir count between $100 \times 10^3/\mu L$ and the lower limit of normal (LLN) ($140 \times 10^3/\mu L$). The subject received ISIS 721744 at 20 mg and had a platelet count of $139 \times 10^3/\mu L$ on Study Day 99; all other reported values for this subject were within the reference range.

Platelet counts will be monitored closely throughout the clinical study.

More complete details can be found in the Investigator's Brochure.

2.5.3. Overall Assessment of Benefit:Risk

No specific risks have been identified with ISIS 721744. The AEs that occurred with the related drug ISIS 546254 were unrelated to reduction of PKK. In addition, the conjugated nature of ISIS 721744 is anticipated to reduce systemic exposure even further. Consequently, the platelet count reductions observed with the higher doses of the unconjugated molecule are not anticipated to occur at the dose tested in this study.

Taking into account the measures taken to minimize risk to patients participating in this study, the potential risks identified in association with ISIS 721744 are justified by the anticipated benefits that may be afforded to patients with HAE.

3. EXPERIMENTAL PLAN

3.1. Study Design

This Phase 2a study will be conducted at multiple Study Centers worldwide to assess the efficacy of ISIS 721744 in approximately 24 patients with HAE. Part A of the study will be randomized, double-blind, and placebo-controlled; Part B of the study will be open-label.

The study will be conducted concurrently in 2 parts (Part A and Part B); patients will be allocated into Part A or Part B according to type of HAE (i.e., either HAE-1/HAE-2 in Part A or HAE-nC1-INH in Part B). Part A is randomized, double-blind, and placebo-controlled; and Part B is open-label. The study visit schedule and procedures are nearly identical in Part A and Part B, and thus are presented together; any differences are indicated where applicable.

In Part A, approximately 18 patients with HAE-1/HAE-2 will be randomized to SC injections of ISIS 721744 80 mg or placebo in a 2:1 ratio (ISIS 721744:placebo). In Part B, approximately 6 patients with HAE-nC1-INH will be administered open-label SC injections of ISIS 721744 80 mg. Due to the rarity of HAE-nC1-INH, enrollment in Part B may be ended early if Study Centers are unable to enroll sufficient patients; this will not impact the completion of Part A.

Patients who discontinue treatment will remain in the study and attend the Early Termination (ET) Visit unless consent is withdrawn.

Detailed information regarding the study procedures is presented in Section 6 and Appendix A. Appendix B includes a list of laboratory analytes required for the study.

3.2. Number of Study Centers

This study will be conducted at multiple Study Centers worldwide.

3.3. Number of Patients

A total of approximately 24 patients in Parts A and B combined will be administered SC injections of ISIS 721744 80 mg or placebo every 4 weeks. Patients will be allocated into Part A or Part B according to type of HAE, (i.e., either HAE-1/HAE-2 or HAE-nC1-INH): approximately 18 patients with HAE-1/HAE-2 are planned to be enrolled in Part A of the study, and, in parallel, approximately 6 patients with HAE-nC1-INH are planned to be enrolled in Part B of the study. Due to the rarity of HAE-nC1-INH, enrollment in Part B may be ended early if Study Centers are unable to enroll sufficient patients with HAE-nC1-INH; this will not impact completion of Part A.

3.4. Overall Study Duration and Follow-up

The study will consist of Screening, Treatment, and Post-Treatment Periods. Please refer to the Schedule of Procedures in Appendix A.

Patients may be required to attend additional visits for monitoring of AEs or abnormal investigation results. The frequency of additional monitoring will be determined by the Sponsor Medical Monitor in consultation with the Investigator.

The length of each patient's participation in the study is approximately 8 months, which includes an up to 8-week Screening Period, a 12-week Treatment Period (patients will receive fixed SC doses of Study Drug every 4 weeks during 4 on-site study visits), and a 4- to 13-week Post-Treatment Period as determined by whether a patient enrolls in the ISIS 721744-CS3 OLE study.

3.4.1. Screening

Patient eligibility for the study will be determined within 8 weeks (56 days) prior to study entry.

3.4.2. Treatment Period

Eligible patients will report to the Study Center for the first administration of Study Drug on Study Day 1 (Week 1 Visit) and will continue to receive Study Drug once every 4 weeks during the 12-week Treatment Period. Patients will also return to the Study Center on Week 3 (or Home Healthcare (if available), as arranged by the Study Center personnel, per the Schedule of Procedures in Appendix A) for a safety monitoring visit.

3.4.3. Post-Treatment Period

Patients are to return to the Study Center for post-treatment follow-up visits (or Home Healthcare (if available), as arranged by the Study Center personnel, per the Schedule of Procedures in Appendix A at Study Weeks 17, 21, and 26/ET. Alternatively, patients who complete Study Visit Week 17, and meet eligibility requirements, may start the treatment period in the ISIS 721744-CS3 OLE study anytime after the Week 17 visit and discontinue participation in the CS2 Post-Treatment Evaluation Period. Patients may be required to attend additional visits for monitoring of AEs or abnormal investigation results. The frequency of additional monitoring will be determined by the Sponsor Medical Monitor in consultation with the Investigator.

The final study visit, for patients not enrolling in the OLE, will be the Week 26/ET Visit.

3.5. End-of-Study

The End-of-Study is defined as the date of the last visit of the last patient in the study.

3.6. Data and Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) will be assembled to review safety, tolerability, and efficacy (as needed) data collected on ISIS 721744 during this study. Based on its ongoing assessment of the safety and tolerability of ISIS 721744, the DSMB will provide recommendations to the Sponsor for modifying, stopping, or continuing the study as planned. Details on the safety assessments, frequency of review, meeting schedules, and controlled access to unblinded data are outlined in the DSMB Charter and Statistical Analysis Plan (SAP).

4. PATIENT ENROLLMENT

4.1. Screening

Before patients may be enrolled into the study, the Sponsor or designee requires a copy of the Study Center's written Independent Ethics Committee (IEC)/Institutional Review Board (IRB) approval of the protocol, informed consent form (ICF), and all other patient information and/or recruitment material.

Patients must sign the consent form before any screening tests or assessments, prior to screening blood draws, are performed. At the time of consent, the patient will be considered enrolled into the study and will be assigned a unique screening number before any study procedures, including screening procedures, are performed. At the time of randomization, patients will be assigned a unique patient identification number. This number will be used to identify the patient throughout the study and must be used on all study documentation related to that patient. The screening number and patient identification number must remain constant throughout the entire study.

In the event the patient is re-consented and re-screened, the patient must be given a new screening number. Screening numbers, once assigned, will not be re-used.

4.2. Randomization

Patients will be allocated into Part A or Part B according to type of HAE (i.e., either HAE-1/HAE-2 in Part A or HAE-nC1-INH in Part B). Only Part A will be randomized and placebo-controlled.

Patients will be enrolled and/or randomized (Part A only) at the Week 1 Visit, after all screening assessments have been completed and after the Investigator has verified that they are eligible per the criteria in Sections 5.1 and 5.2. No patient may begin treatment prior to randomization (Part A only) and assignment of a unique patient identification number.

In Part A, approximately 18 patients with HAE-1/HAE-2 will be randomized via the Interactive Response Technology (IRT) system to SC injections of ISIS 721744 80 mg or placebo in a 2:1 ratio (ISIS 721744:placebo). In Part B, approximately 6 patients with HAE-nC1-INH will be enrolled via the IRT system to receive open-label SC injections of ISIS 721744 80 mg. Due to the rarity of HAE-nC1-INH, enrollment in Part B may be ended early if Study Centers are unable to enroll sufficient patients; this will not impact the completion of Part A.

Randomization information will be concealed from the Investigators and patients until the end of the study, with the exception of an emergency situation involving a patient that requires unblinding of the treatment assignment.

Both ISIS 721744 and placebo will be provided as injections for SC administration and will be identical in appearance.

4.3. Replacement of Patients

Patients who withdraw from the study will not be replaced.

Patients whose randomization code has been broken will not be replaced.

4.4. Unblinding of Treatment Assignment

For Part A, the Sponsor and all patients, monitors, and Study Center personnel related to the study will be blinded throughout the study. However, if a patient has suffered an SAE (as defined in Section 9.3.3), and/or when knowledge of the treatment assignment will impact the clinical management of the patient, the Investigator will have the ability to unblind the treatment assignment for that patient via the IRT system.

In the case of unblinding, the IRT system will send a blinded notification to the Sponsor or designee within 24 hours to let them know that a patient was unblinded. In addition, all suspected unexpected serious adverse reactions (SUSARs) will be unblinded by the Sponsor or designee for the purpose of regulatory reporting (see Section 9.2).

Every reasonable attempt should be made to complete the ET study procedures and observations (see Appendix A) prior to unblinding, as knowledge of the treatment arm could influence patient assessment.

5. PATIENT ELIGIBILITY

To be eligible to participate in this study candidates must meet the following eligibility criteria within 8 weeks (56 days) of the Week 1 Visit (Study Day 1) or at the time point specified in the eligibility criteria listed.

5.1. Inclusion Criteria

1. Patients must provide written informed consent (signed and dated) and any authorizations required by local law and be able to comply with all study requirements for the duration of the study.
2. Patients must be aged ≥ 18 years at the time of informed consent.
3. Patients must have a documented diagnosis of HAE-1/HAE-2 (for inclusion in Part A) or HAE-nC1-INH (for inclusion in Part B) as defined below:
    a. Documented diagnosis of HAE-1/HAE-2 based upon ALL of the following:
        i. Documented clinical history consistent with HAE (SC or mucosal, non-pruritic swelling episodes without accompanying urticaria) (Maurer et al. 2018).
        ii. Diagnostic testing results that confirm HAE-1/HAE-2: C1-INH functional level < 40% normal level. Patients with a functional level of 40% to 50% of normal can be enrolled if their complement factor C4 (C4) level is below the LLN or if a known pathogenic mutation in the *SERPING1* gene has been demonstrated.
        iii. At least 1 of the following: age at reported HAE onset ≤ 30 years; a family history consistent with HAE-1/HAE-2; or complement component 1q within the normal range.
    b. Documented diagnosis of HAE-nC1-INH based upon documented clinical history consistent with HAE (SC or mucosal, non-pruritic swelling episodes without accompanying urticaria) (Maurer et al. 2018) AND any 1 of the following:
        i. A clinical diagnosis of BK-mediated angioedema as confirmed with threshold-stimulated kallikrein activity and Investigator-confirmed response to acute use of a BK targeted treatment (icatibant or ecallantide).
        ii. One (1) of the established mutations (c.1032C>A, Thr309Lys; c.1032C>G, Thr309Arg; c.971_1018+24del72*; or c.892_909dup) in the factor XII gene.
        iii. The established mutation in the plasminogen gene (c.988A>G, p.Lys330Glu).
        iv. The established mutation in the angiopoietin-1 gene (c.355G>T, p.A119S).
4. Patients must:
    a. Experience a minimum of 2 HAE attacks (assessed by the Angioedema Activity Score [AAS] and confirmed by the Investigator) during the Screening Period.
    b. Complete the AAS questionnaire on a daily basis (minimum of 4 daily assessments per week) for the duration of the Screening Period.

5. Patients must have access to, and the ability to use, ≥ 1 acute medication(s) (e.g., plasma-derived or recombinant C1-INH concentrate or a BK2-receptor antagonist) to treat angioedema attacks.
6. Female patients must be non-pregnant (and not planning a pregnancy during the study) and non-lactating, and be either:
   a. Surgically sterile (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy, or bilateral oophorectomy).
   b. Post-menopausal (defined as 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years of age, 12 months of spontaneous amenorrhea without an alternative medical cause and follicle-stimulating hormone [FSH] levels in the post-menopausal range for the laboratory involved).
   c. Abstinent (only acceptable as true abstinence, i.e., when in line with the preferred and usual lifestyle of the patient; periodic abstinence [e.g., calendar, ovulation, symptothermal, or post-ovulation methods], declaration of abstinence for the duration of the study, or withdrawal are not acceptable methods of contraception).
   d. If engaged in sexual relations of childbearing potential, agree to use highly effective contraceptive methods (refer to Section 6.3.1) from the time of signing the ICF until at least 24 weeks after the last dose of Study Drug (ISIS 721744 or placebo).
7. Male patients must be surgically sterile or, if engaged in sexual relations with a female of childbearing potential, the patient must agree to use a highly effective contraceptive method (refer to Section 6.3.1) from the time of signing the ICF until at least 24 weeks after the last dose of Study Drug (ISIS 721744 or placebo).

5.2. Exclusion Criteria

1. Anticipated use of short-term prophylaxis for angioedema attacks for a pre-planned procedure during the Screening or Study Periods.
2. Concurrent diagnosis of any other type of recurrent angioedema, including acquired or idiopathic angioedema.
3. Anticipated change in the use of concurrent androgen prophylaxis used to treat angioedema attacks.
4. Any clinically significant abnormalities in screening laboratory values that would render a patient unsuitable for inclusion in the study. The following values are exclusionary:
   a. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 2.5 × upper limit of normal (ULN).
   b. Bilirubin > 1.5 × ULN unless due to Gilbert's syndrome.
   c. Platelet count < LLN.
   d. Estimated glomerular filtration rate (eGFR) < 60 mL/min (as determined by the Cockcroft-Gault Equation for creatinine clearance).
   e. aPTT > 1.5 × ULN

5. Patients with a history of acquired coagulopathies or bleeding diathesis (e.g., thrombocytopenia, disseminated intravascular coagulation, coagulopathy of liver disease, drug-induced platelet dysfunction, hyperfibrinolysis, acquired clotting factor inhibitors) and inherited bleeding disorders (e.g., hemophilia A, hemophilia B, other clotting factor deficiencies, qualitative platelet disorders, inherited thrombocytopenia, vascular abnormalities).
6. Any clinically significant renal or hepatic diseases.
7. Active infection requiring systemic antiviral or antimicrobial therapy that will not be completed prior to dosing.
8. Active infection with HIV, hepatitis C or hepatitis B diagnosed by initial serological testing and confirmed with RNA testing, or prior treatment for hepatitis C. Patients at Screening who test positive by serology, but negative by RNA may be allowed in consultation with the Sponsor Medical Monitor.
9. Malignancy within 5 years, except for basal or squamous cell carcinoma of the skin or carcinoma *in situ* of the cervix that has been successfully treated.
10. Treatment with another investigational drug or biological agent within 1 month or 5 half-lives, whichever is longer, of Screening.
11. Exposure to any of the following medications:
    a. Angiotensin-converting enzyme (ACE) inhibitors or any estrogen-containing medications with systemic absorption (such as oral contraceptive or hormonal replacement therapy) within 4 weeks prior to Screening.
    b. Chronic prophylaxis with lanadelumab within 10 weeks prior to Screening.
    c. Oligonucleotides (including small interfering RNA) within 4 months of Screening if single dose received, or within 12 months of Screening if multiple doses received.
12. Any condition that, in the opinion of the Investigator, may compromise the patient's safety or compliance, preclude successful conduct of the study, or interfere with the interpretation of results.

6. STUDY PROCEDURES

6.1. Study Schedule

The study will be conducted concurrently in 2 parts (Part A and Part B); patients will be allocated into Part A or Part B according to type of HAE (i.e., either HAE-1/HAE-2 in Part A or HAE-nC1-INH in Part B). Part A is randomized, double-blind, and placebo-controlled; and Part B is open label. The study visit schedule and procedures are nearly identical in Part A and Part B, and thus are presented together; any differences are indicated where applicable.

All required study procedures are outlined in Appendix A.

The safety of ISIS 721744 will be continually monitored throughout the study by the Investigator and the Sponsor Medical Monitor.

The length of each patient's participation from Screening to the last study visit is up to approximately 8 months (231 days).

6.1.1. Screening

Written informed consent for the study will be obtained prior to the performance of any study-related procedures, including screening procedures. A 56-day period is provided for completing screening assessments and determining patient eligibility for the study.

Safety labs may be retested for determination of patient eligibility at the Investigator's discretion. The Sponsor Medical Monitor will be available for consultation, if needed.

After providing written informed consent, patients will be screened for eligibility criteria. During the Screening Period, the following assessments will be performed: demographics; medical history, including a detailed HAE history; prior and concomitant medications, including type of prophylaxis (if used) and type of acute treatment; HIV, hepatitis B, and hepatitis C screening; pregnancy testing for women of childbearing potential (WOCBP) and FSH testing for confirmation of menopause per inclusion criteria; quality of life as assessed by the AE-QoL questionnaire; attack frequency, as assessed by the AAS daily during up to 8 consecutive weeks, and confirmed by the Investigator; HAE attack assessment; physical examinations, including vital signs, body height, and weight; ECGs; AEs; PD blood sampling; inflammatory panel; and clinical laboratory assessments (chemistry, hematology, coagulation, and urinalysis).

Threshold-stimulated kallikrein activity will be assessed only in patients who have HAE-nC1-INH without a factor XII mutation or the plasminogen or angiopoietin-1 mutation. Genetic testing will be performed only for patients who do not have HAE genetic diagnostic testing results prior to Screening. During the Screening Period, patients must experience a minimum of 2 HAE attacks (assessed by the AAS and confirmed by the Investigator) to be eligible for the study; patients will be instructed to report details of any HAE attack to the study site within 72 hours of the onset of the attack. Throughout the Screening Period, site personnel will contact the patient once a week (at approximately 7 days after the last contact with the patient) in order to inquire about any attack that may have occurred. If a patient experiences a third attack, the patient should be randomized as soon as possible, assuming all other screening activities have been completed and the patient meets all other eligibility requirements; in such cases, the Screening Period may be shorter than 8 weeks.

During the course of the study, the use of acute medications (plasma-derived or recombinant C1-INH concentrate, BK2-receptor antagonist, or kallikrein inhibitor) to treat angioedema attacks is allowed as medically indicated. Patients can be treated with on-demand therapy as determined by their treating physician.

6.1.2. Treatment Period

After a Screening Period of up to 8 weeks, those patients who had at least 2 documented attacks (assessed by the AAS and confirmed by the Investigator) during the Screening Period and met all other eligibility criteria will be administered Study Drug (ISIS 721744 or placebo). Patients in Part A will be randomized to receive ISIS 721744 80 mg or placebo every 4 weeks for a total Treatment Period of 12 weeks. Patients in Part B will all receive open-label ISIS 721744 80 mg every 4 weeks for a total Treatment Period of 12 weeks.

Study Drug will be administered as SC injections in the abdomen, thigh, or outer area of the upper arm by qualified personnel at the Study Center or by Home Healthcare professional (if available

and after dosing instructions and training are provided by qualified site personnel). The first dose of Study Drug will be administered at the Study Center on Study Day 1 (Week 1 Visit). Study Center personnel (or Home Healthcare if available), will complete procedures per the Schedule of Procedures in Appendix A. A ± 2-day excursion from the scheduled visit date is permitted for all visits (excluding the Week 1 Visit on Study Day 1) during the Treatment Period.

During the study, patients will be instructed to report details of any HAE attack to the study site within 72 hours of the onset of the attack. During the Treatment Period, the following data will be collected: daily AAS and number of HAE attacks (assessed by the AAS and confirmed by the Investigator); number of HAE attacks that required on-demand treatment; HAE attack details, including localization, severity, course, and details of any required treatment (i.e., frequency and dose); and vital signs. Throughout the Treatment Period, site personnel will contact the patient once a week (at approximately 7 days after the last contact with the patient) in order to inquire about any attack that may have occurred. In addition, at study visit time points, site personnel will inquire about any new HAE attack information that was not provided through patient contact with the site. See Section 6.2.1 for further information on the collection of data surrounding HAE attacks. Additional assessments will be performed throughout the Treatment Period as indicated in the Schedule of Procedures table in Appendix A.

Additionally, blood will be collected to assess PD and coagulation parameters, including, but not limited to: plasma PKK, plasma proenzyme activation, cHK levels, D-dimer levels, aPTT, plasmin-antiplasmin complexes, C4 split products, and platelet counts. Blood samples will also be collected regularly throughout the study for safety and PK/PD analyses.

Patients who discontinue treatment will remain in the study and attend the ET Visit unless consent is withdrawn.

Detailed information regarding the study procedures is presented in Section 6 and Appendix A. Appendix B includes a list of laboratory analytes required for the study. Detailed information regarding PK subgroups and collection times is provided in Appendix C.

6.1.3. Post-Treatment Period

Each patient will be followed for safety assessments for up to 13 weeks after the last dose of Study Drug. During the Post-Treatment Period, patients will return to the Study Center (or have Home Healthcare (if available), as arranged by the Study Center personnel, per the Schedule of Procedures in Appendix A) for visits at Weeks 17, 21, and 26/ET for safety and clinical laboratory evaluations and for blood sampling for PK/PD analyses. A ± 2-day excursion from the scheduled visit date is permitted for the visits at Weeks 17 and 21, and a ± 3-day excursion from the scheduled visit date is permitted for the visit at Week 26/ET. Alternatively, after completion of the Week 13 visit, eligible patients may elect to enroll in the ISIS 721744-CS3 OLE study, pending study approval by the IRB/IEC and the appropriate regulatory authority, and will need to sign the Institutional Review Board/Independent Ethics Committee (IRB/IEC) approved informed consent. Patients who complete Study Visit Week 17, and meet eligibility requirements, may start the treatment period in the CS3 study anytime after the Week 17 visit and discontinue participation in the CS2 Post-Treatment Evaluation Period.

During the Post-Treatment Period, the following data will be collected: daily AAS and number of HAE attacks (assessed by the AAS and confirmed by the Investigator); number of HAE

attacks that required on-demand treatment; HAE attack details, including localization, severity, course, and details of any required treatment (i.e., frequency and dose); and vital signs. Throughout the Post-Treatment Period, site personnel will contact the patient once a week (at approximately 7 days after the last contact with the patient) in order to inquire about any attack that may have occurred. In addition, during study visits, site personnel will inquire about any new HAE attack information that was not provided through patient contact with the site. See Section 6.2.1 for further information on the collection of data surrounding HAE attacks.

Additionally, blood will be collected to assess PD and coagulation parameters, including, but not limited to: plasma PKK, plasma proenzyme activation, cHK levels, D-dimer levels, aPTT, plasmin-antiplasmin complexes, C4 split products, and platelet counts. Blood samples will also be collected regularly throughout the study for safety and PK/PD analyses. Additional assessments will be performed throughout the Post-Treatment Period as indicated in the Schedule of Procedures table in Appendix A.

Patients who withdraw early from the study during the Treatment Period will be required to complete their End-of-Study evaluations following procedures listed for the Week 26/ET Visit; see Appendix A.

6.2. Study Assessments

6.2.1. Collection of Hereditary Angioedema Attack Details

Historical HAE attack information will be collected at Screening. During the study, patients will be instructed to report details of any HAE attack to the study site within 72 hours of the onset of the attack. Throughout the Screening, Treatment, and Post-Treatment Periods, site personnel will contact the patient once a week (at approximately 7 days after the last contact with the patient) in order to inquire about any attack that may have occurred. In addition, during study visits, site personnel will inquire about any new HAE attack information that was not provided through patient contact with the site.

During the Screening, Treatment, and Post-Treatment Periods, detailed information on each HAE attack will be collected, and the number of HAE attacks that required on-demand treatment, and the details of any on-demand treatment used (frequency and dosing), will be assessed. For each HAE attack, the following data will be collected:

- Date/time of symptom onset
- Description of symptoms
- Location and description of symptoms:
  - Peripheral angioedema: cutaneous swelling involving an extremity, face, neck, torso, and/or genitourinary region
  - Abdominal angioedema: abdominal pain, with or without abdominal distension, nausea, vomiting, or diarrhea
  - Laryngeal angioedema: stridor, dyspnea, difficulty speaking, difficulty swallowing, throat tightening, or swelling of the tongue, palate, uvula, or larynx

- HAE attack severity:
  - Mild: transient or mild discomfort
  - Moderate: mild to moderate limitation in activity, some assistance needed
  - Severe: marked limitation in activity, assistance required
- Need for assistance, medical intervention, emergency room visit, or hospitalization
- Medications to treat the attack
- HAE attack course, including if the HAE attack(s) in question was a typical attack for the patient, or if there was an alternative diagnosis
- Date/time symptoms resolved

An HAE attack will be defined as an event with signs or symptoms consistent with an attack in at least 1 of the locations noted above. A discrete attack will be counted if there is an at least 24-hour symptom-free period between attacks.

6.2.2. Patient-Reported Outcomes

6.2.2.1. Angioedema Quality of Life Questionnaire

Quality of life will be assessed by the AE-QoL questionnaire during Screening and at Weeks 1, 9, 17, and 26/ET.

The AE-QoL questionnaire is a validated tool to assess symptom-specific health-related quality of life impairment in patients suffering from recurrent angioedema (Weller et al. 2013). The AE-QoL is a self-administered questionnaire that can be completed in less than 5 minutes; it comprises 17 questions across 4 domains: functioning, fatigue/mood, fears/shame, and food. The AE-QoL can be used to calculate scores for the 4 individual domains, and can also be used to determine a total score. The AE-QoL will be completed by the patient.

6.2.2.2. Angioedema Activity Score

Patients will be instructed on the use of the AAS questionnaire during Screening and will record their HAE attacks using the AAS questionnaire during the Screening Period to confirm study eligibility. The AAS questionnaire will be completed by patients on a daily basis (minimum of 4 daily assessments per week) for the duration of the study.

During the Screening Period, patients must experience a minimum of 2 HAE attacks (assessed by the AAS and confirmed by the Investigator) to be eligible for the study.

Enrolled patients will continue to record HAE attacks using the AAS questionnaire throughout the Treatment and Post-Treatment Periods.

The AAS is a validated patient-reported outcome instrument to assess disease activity in patients with recurrent angioedema. The AAS was designed as a diary-type tool, and is easy to administer and fast to complete. Using the AAS questionnaire, patients score each of 5 key symptom-related factors from 0 to 3, resulting in a total daily score of 0 to 15. Daily AAS can be summed to provide scores every 7 days, every 4 weeks, and every 12 weeks (Weller et al. 2013).

6.2.3. Laboratory Assessments

Laboratory analyte samples will be collected throughout the study. A list of these analytes is contained in Appendix B.

If the platelet value, serum creatinine, or liver enzyme tests are uninterpretable (e.g., due to clumping, hemolysis, or quantity not sufficient) or missing, a repeat blood specimen should be re-drawn as soon as possible (ideally within 7 days) either in clinic or by Home Healthcare or local laboratory.

6.3. Restriction on the Lifestyle of Patients

6.3.1. Contraception Requirements

All male patients and WOCBP must refrain from sperm/egg donation and either be abstinent† or use highly effective contraception from the time of signing the ICF until at least 24 weeks after their last dose of Study Drug.

For male patients engaged in sexual relations with a WOCBP, if their female partner is using highly effective contraception from the time of the patient signing the informed consent until 24 weeks after the patient's last dose of study treatment, then it is not required for the male patient to also use a highly effective contraceptive method.

For the purposes of this study, a WOCBP is defined as any female who has experienced menarche, and who does not meet 1 of the following conditions:

- Post-menopausal: 12 months of spontaneous amenorrhea in females > 55 years of age or, in females ≤ 55 years, 12 months of spontaneous amenorrhea without an alternative medical cause and FSH levels in the post-menopausal range for the laboratory involved
- 6 weeks after surgical bilateral oophorectomy with or without hysterectomy
- Post-hysterectomy

For the purposes of the study, highly effective contraception is defined as follows:

For male patients:

- Highly effective male contraception includes a vasectomy with negative semen analysis at follow-up, or the non-pregnant female partner of childbearing potential uses a highly effective contraceptive method (defined below).
- Male patients with partners that are pregnant must use condoms as contraception to ensure that the fetus is not exposed to the Study Drug.

Note: A female condom and a male condom should not be used together as friction between the two can result in either or both products failing.

For female patients and female partners of male patients, highly effective contraception methods comprise

- Surgical sterilization (i.e., bilateral tubal occlusion); progestogen-only hormonal contraception associated with inhibition of ovulation; intrauterine contraception device or intrauterine hormone-releasing system.

†**Note:** Abstinence (i.e., refraining from heterosexual intercourse throughout the duration of study participation) is only acceptable as true abstinence, i.e., when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation methods), declaration of abstinence for the duration of the study, or withdrawal are not acceptable methods of contraception.

7. STUDY DRUG

7.1. Study Drug Description

Study Drug (ISIS 721744 or placebo) characteristics are listed in Table 1.

The Study Drug (ISIS 721744 or placebo) is contained in 2-mL stoppered glass vials. The Study Drug (ISIS 721744 or placebo) and its storage and preparation instructions will be provided by the Sponsor or designee. The Study Drug (ISIS 721744 or placebo) must be stored securely at 2 °C to 8 °C and be protected from light.

During the Treatment Period, Study Drug (ISIS 721744 or placebo) will be administered as a single-SC injection every 4 weeks.

Table 1: Study Drug Characteristics

Study Drug	**ISIS 721744**	**Placebo**
Strength	100 mg/mL	Not Applicable
Volume/Formulation	0.8 mL solution per vial	0.8 mL solution per vial
Route of Administration	SC	SC

7.2. Packaging and Labeling

The Sponsor will provide the Investigator with packaged Study Drug (ISIS 721744 or placebo) labeled in accordance with specific country regulatory requirements.

7.3. Study Drug Accountability

The study staff is required to document the receipt, dispensing, and return/destruction of Study Drug (ISIS 721744 or placebo) supplies provided by the Sponsor according to Sponsor instruction and in accordance with institutional policy.

8. TREATMENT OF PATIENTS

8.1. Study Drug Administration

Study Drug (ISIS 721744 or placebo) will be administered as a single-SC injection once every 4 weeks by blinded study staff during on-site visits at the Study Centers or by Home Healthcare professional (if available and after dosing instructions and training are provided by qualified site personnel). Vials of Study Drug (ISIS 721744 or placebo) are for single use only.

Please refer to the Study Drug Manual provided by the Sponsor or designee for more detailed instructions for Study Drug (ISIS 721744 or placebo) preparation and administration.

8.2. Other Protocol-Required Drugs

Patients must have access to, and the ability to use, ≥ 1 acute medication(s) (e.g., plasma-derived or recombinant C1-INH concentrate or a BK2-receptor antagonist) to treat angioedema attacks. During the course of the study, the use of acute medications (plasma-derived or recombinant C1-INH concentrate, BK2-receptor antagonist, or kallikrein inhibitor) to treat angioedema attacks is allowed as medically indicated. Patients can be treated with on-demand therapy as determined by their treating physician.

8.3. Other Protocol-Required Treatment Procedures

There are no other protocol-required treatment procedures.

8.4. Treatment Precautions

There are no specific treatment precautions required.

8.5. Safety Monitoring Rules

Please refer also to the "Guidance for Investigator" section of the Investigator's Brochure.

For the purposes of safety monitoring, Baseline is defined as the average of the pre-dose Study Day 1 value and the last value prior to Study Day 1.

In addition to the standard monitoring of clinical safety parameters, the following guidelines are provided for the monitoring of selected parameters chosen based on preclinical and clinical observations.

Confirmation Guidance: At any time during the study (Treatment or Post-Treatment Periods), the initial clinical laboratory results meeting the safety monitoring criteria presented below **must be confirmed** by performing measurements (ideally in the same laboratory that performed the initial measurement) on new specimens. All new specimen collections should take place as soon as possible (ideally within 3 days of the initial collection). For stopping rules, if the initial laboratory result is observed during the Treatment Period, the results from the retest **must be available** prior to administering the next dose of Study Drug (ISIS 721744 or placebo).

Re-dosing Guidance: Patients with initial laboratory test values that reach a stopping rule must not be re-dosed until the retest results are available. In general, patients who do not meet the stopping rules based upon retest may continue dosing. However, the Investigator and the

Sponsor Medical Monitor (or appropriately qualified designee) should confer as to whether additional close monitoring of the patient is appropriate. If any of the stopping criteria described below (refer to Section 8.6) are met, the patient will be permanently discontinued from further treatment with Study Drug (ISIS 721744 or placebo), evaluated fully as outlined below and in consultation with the Sponsor Medical Monitor or appropriately qualified designee, and will be followed up in accordance with Section 8.8 of the protocol.

8.5.1. Safety Monitoring Rules for Liver Chemistry Tests

The following rules are adapted from the draft guidance for industry, "Drug-Induced Liver Injury: Premarketing Clinical Evaluation," issued by the U.S. Department of Health and Human Services, Food and Drug Administration, July 2009. For a definition of Baseline, please refer to guidance in Section 8.5 above.

In the event of an ALT or AST measurement that is > 3 × ULN (or the greater of 2 × baseline value or 3 × ULN if the baseline value was > ULN) at any time during the study (Treatment or Post-Treatment Period), the initial measurement(s) should be confirmed as described above. Additional, confirmatory measurements should also be performed if ALT or AST levels increase to 5 × ULN.

Frequency of Repeat Measurements: Patients with confirmed ALT or AST levels > 3 × ULN (or the greater of 2 × baseline value or 3 × ULN if the baseline value was > ULN) should have their liver chemistry tests (ALT, AST, alkaline phosphatase, international normalized ratio [INR], and total bilirubin) retested at least once-weekly until ALT and AST levels become ≤ 1.2 × ULN or 1.2 × baseline value if the baseline value was > ULN.

Further Investigation into Liver Chemistry Elevations: For patients with confirmed ALT or AST levels > 3 × ULN (or the greater of 2 × baseline value or 3 × ULN if the baseline value was > ULN), the following evaluations should be performed:

- Obtain a more detailed history of symptoms and prior and concurrent diseases
- Obtain further history for concomitant drug use (including non-prescription medications, herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
- Obtain a history for exposure to environmental chemical agents and travel
- Perform serology for viral hepatitis (hepatitis A virus immunoglobulin M ([IgM], hepatitis B surface antigen, hepatitis C virus antibody, cytomegalovirus IgM, and Epstein-Barr Virus antibody panel)
- Perform serology for autoimmune hepatitis (e.g., antinuclear antibody)

Additional liver evaluations, including gastroenterology/hepatology consultations, hepatic computed tomography or magnetic resonance imaging scans, may be performed at the discretion of the Investigator, in consultation with the Sponsor Medical Monitor. Repetition of the above evaluations should be considered if a patient's ALT and/or AST levels reach 5 × ULN.

8.5.2. Safety Monitoring Rules for Platelet Count Results

Please refer also to Table 2.

Platelet count will be monitored at least every 4 weeks during the Treatment and Post-Treatment Periods. The Investigator should review all platelet count results within 48 hours of receipt. Any unreportable platelet count result must be rechecked ideally within 7 days and determined not to have met a stopping rule before dosing can continue. If a patient's platelet count falls to 100,000/mm^3 or less, then the patient's platelet counts should be monitored weekly. In case of platelet reduction to below 75,000/mm^3, the platelet monitoring rule defined in stopping rules (Section 8.6.2) should be followed.

In the event of a platelet count < 75,000/mm^3, additional laboratory investigations may be conducted in consultation with the Sponsor Medical Monitor.

8.5.3. Safety Monitoring Rules for Renal Function Test Results

If a patient's results meet Criteria 1 or 2 below, the Investigator should confirm the results and initiate weekly monitoring if confirmed. If the event of a persistent elevation is observed over 2 consecutive weeks, then go to Section 8.6.3.

1. Serum creatinine increase that fulfills all of the following: ≥ 0.3 mg/dL (26.5 µmol/L) and ≥ 40% above baseline creatinine values and > ULN (refer to definition of Baseline in Section 8.6)
2. Proteinuria, urine protein/creatinine ratio > 750 mg/g for baseline values ≥ 200 mg/g, or 4 × baseline value for baseline values < 200 mg/g that are confirmed by repeated urine protein/creatinine ratio or by a quantitative total urine protein measurement of > 1.0 g/24 hours

8.5.4. Safety Monitoring for Minor Bleeding Events

If a bleeding event occurs, including minor bleeding events such as excess bruising, petechiae, or gingival bleeding on brushing teeth, the Investigator should notify the Sponsor Medical Monitor and additional testing of coagulation parameters (aPTT, PT, and INR) and platelet count should be performed.

8.6. Stopping Rules

For the purposes of the stopping rules, Baseline is defined as the average of the pre-dose Study Day 1 value and the last value prior to Study Day 1.

8.6.1. Stopping Rules for Liver Chemistry Elevations

In the event of laboratory results meeting the following criteria, **and the event is without an alternative explanation as discussed with the Sponsor Medical Monitor,** dosing of a patient with Study Drug (ISIS 721744 or placebo) will be stopped permanently; values that are not confirmed due to failure to retest or missing lab values will be presumed confirmed:

1. ALT or AST > 8 × ULN, which is confirmed
2. ALT or AST > 5 × ULN, which is confirmed and persists for ≥ 2 weeks
3. ALT or AST > 3 × ULN (or the greater of 2 × baseline value or 3 × ULN if the baseline value was > ULN), which is confirmed **and** total bilirubin > 1.5 × ULN or INR > 1.5

4. ALT or AST > 3 × ULN (or the greater of 2 × baseline value or 3 × ULN if the baseline value was > ULN), which is confirmed, **and** the new appearance (i.e., onset coincides with the changes in hepatic enzymes) of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or concomitant eosinophilia (> ULN)

8.6.2. Stopping Rules for Platelet Count Results

Please refer also to Table 2.

In the event of any platelet count < 25,000/mm^3, dosing of the patient with Study Drug will be stopped permanently. Platelet count should be monitored daily until 3 successive values > 25,000/mm^3. Then, monitor twice weekly until 3 successive values > 75,000/mm^3. Then, monitor weekly until 3 successive values > 100,000/mm^3. Consider more frequent monitoring if additional risk factors for bleeding are present (see Table 2). Administration of steroids is strongly recommended for patients whose platelet count is < 25,000/mm^3. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend dexamethasone 40 mg daily for 4 days every 2 to 4 weeks for 1 to 4 cycles; prednis(ol)one 0.5 to 2 mg/kg/day for 2 to 4 weeks then taper; or methylprednisolone 30 mg/kg/day for 7 days. (**Note:** Patient may require continuation with oral steroids after methylprednisolone).

In the event of a platelet count ≥ 25,000/mm^3 to < 50,000/mm^3, dosing of the patient with Study Drug will be stopped permanently. Platelet count should be monitored twice weekly until 3 successive values > 75,000/mm^3. Then, monitor weekly until 3 successive values > 100,000/mm^3. Consider more frequent monitoring and/or the administration of steroids if additional risk factors for bleeding are present (see Table 2).

In the event of a platelet count ≥ 50,000/mm^3 to < 75,000/mm^3, and in the absence of major bleeding or clinically relevant non-major bleeding (defined below), dosing with Study Drug should be suspended temporarily until the platelet count has recovered to > 100,000/mm^3. The suitability of the patient for continued dosing will be determined by the Investigator in consultation with the Sponsor Medical Monitor and will be based on factors such as the original rate of decline in the patient's platelet count, whether any bleeding events were experienced, and the speed of recovery of platelet count after interruption of dosing. Platelet count must be measured twice weekly until 3 successive values > 75,000/mm^3, then weekly until 3 successive values > 100,000/mm^3. Consider more frequent monitoring if additional risk factors for bleeding are present (see Table 2). Any unreportable platelet count result must be rechecked, ideally within 7 days, and determined not to have met a stopping rule before dosing can continue.

Definition of Major Bleeding Events (Schulman and Kearon 2005)

1. Fatal bleeding, and/or
2. Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarterial or pericardial, or intramuscular with compartment syndrome, and/or
3. Clinically overt bleeding leading to transfusion of ≥ 2 units of packed red blood cells or whole blood or a fall in hemoglobin of ≥ 2.0 g/dL (1.24 mmol/L) within 24 hours

Definition of Clinically Relevant Non-Major Bleeding Events

Clinically relevant non-major bleeding is defined as overt bleeding not meeting the criteria for major bleeding but that resulted, for example, in medical examination, intervention, or had clinical consequences for a patient.

Definition of Minor Bleeding Events

Minor bleeding events are those that do not fulfill the criteria for major bleeding or clinically relevant, non-major bleeding events (defined above), for example excess bruising, petechiae, or gingival bleeding on brushing teeth.

If the subsequent test confirms the initial test result, then monitoring frequency and dosing should be adjusted as recommended in Table 2.

Table 2: Actions in Patients with Low Platelet Count

Platelet count (K/mm^3)	Dosing	Monitoring frequency
> 100	Dosing every 4 weeks should be continued.	At least every 4 weeks.
≥ 75 to ≤ 100	Dosing every 4 weeks should be continued.	Every week.
≥ 50 to < 75	Pause dosing. When platelet count returns to > $100K/mm^3$, restart dosing only if approved by the Sponsor Medical Monitor.	Twice weekly until 3 successive values > $75K/mm^3$, then weekly until 3 successive values > $100K/mm^3$. Consider more frequent monitoring if additional risk factors for bleeding are present.‡
≥ 25 to < 50	Permanently discontinue Study Drug. Consider corticosteroids if additional risk factors for bleeding are present.‡	Twice weekly until 3 successive values > $75K/mm^3$, then weekly until 3 successive values > $100K/mm^3$. Consider more frequent monitoring if additional risk factors for bleeding are present.‡
< 25	Permanently discontinue Study Drug. Corticosteroids strongly recommended.*	Daily until 3 successive values > $25K/mm^3$, then twice weekly until 3 successive values > $75K/mm^3$, then weekly until 3 successive values > $100K/mm^3$. Consider more frequent monitoring if additional risk factors for bleeding are present.‡

‡ Additional risk factors for bleeding include age > 60 years, receiving anticoagulant or antiplatelet medicinal products, and/or prior history of major bleeding events.

* It is strongly recommended that, unless corticosteroids are contraindicated, the patient receives glucocorticoid therapy to reverse the platelet decline as recovery in platelet count may be accelerated by administration of high-dose steroids. Treatment guidelines for immune thrombocytopenia (Provan et al. 2010) recommend dexamethasone 40 mg daily for 4 days every 2 to 4 weeks for 1 to 4 cycles; prednis(ol)one 0.5 to 2 mg/kg/day for 2 to 4 weeks then taper; or methylprednisolone 30 mg/kg/day for 7 days (**Note:** patient may require continuation with oral steroids after methylprednisolone).

8.6.3. Temporary Stopping Rules for Renal Function Test Results

In the event of a persistent elevation that is observed over 2 consecutive weeks, for either of the 2 criteria below, dosing of a patient with Study Drug (ISIS 721744 or placebo) may be stopped temporarily:

1. Serum creatinine increase that fulfills all of the following criteria: ≥ 0.3 mg/dL (26.5 µmol/L) and ≥ 40% above baseline creatinine values and > ULN (refer to definition of Baseline in Section 8.6)
2. Proteinuria, dipstick 2 + (confirmed by dipstick retest and then further confirmed by a quantitative total urine protein measurement of > 1.0 g/24 hours)

The possible dosing reinitiation or follow-up schedule for any events meeting either of these criteria will be determined by the Investigator **in consultation with** the Sponsor Medical Monitor or designee.

8.7. Adjustment of Dose and/or Treatment Schedule

Adjustment of dose and/or schedule is not permitted.

8.8. Discontinuation of Study Drug

A patient must permanently discontinue study treatment for any of the following:

- The patient becomes pregnant. Report the pregnancy according to instructions in Section 9.5.4.
- The patient withdraws consent.
- The patient withdraws from treatment (but does not withdraw consent).
- The patient experiences an AE that necessitates permanent discontinuation of Study Drug.
- The patient develops laboratory test abnormalities that meet any of the stopping rules listed in Sections 8.6.1, 8.6.2, or 8.6.3.
- The patient experiences an AE that necessitates unblinding of the Investigator or Sponsor to the patient's treatment assignment.

The reason for discontinuation of Study Drug must be recorded in the electronic Case Report Form (eCRF) and source documentation.

Patients who discontinue Study Drug will remain in the study and attend the ET Visit (Week 17 visit assessments), unless consent is withdrawn. Any patient who discontinues early from the Treatment Period or from the Post-Treatment Follow-Up Period should be strongly encouraged to complete follow-up study visits, procedures and observations (see Appendix A).

8.9. Withdrawal of Patients from the Study Procedures

Patients must be withdrawn from study procedures for any of the following:

- Withdrawal of consent
- The patient is unwilling or unable to comply with the protocol

Other reasons for withdrawal of patients from the study may include the following:

- At the discretion of the Investigator for medical reasons
- At the discretion of the Investigator or Sponsor for non-compliance
- Significant protocol deviation

All efforts will be made to complete and report the observations as thoroughly as possible up to the date of withdrawal. All information, including the reason for withdrawal from study, must be recorded in the eCRF.

Any patient who withdraws consent to participate in the study will be removed from further treatment and study observation immediately upon the date of request. These patients should be encouraged to complete the ET study procedures (Week 17 visit assessments) and observations at the time of withdrawal (see Appendix A).

For patients withdrawn for reasons other than withdrawal of consent, every effort should be made to complete the ET study procedures and observations at the time of withdrawal (see Appendix A).

8.10. Concomitant Therapy and Procedures

The use of concomitant therapies or procedures defined below must be recorded on the patient's eCRF. Adverse events related to administration of these therapies or procedures must also be documented on the appropriate eCRF.

8.10.1. Concomitant Therapy

A concomitant therapy is any non-protocol-specified drug or substance (including over-the-counter medications, herbal medications, and vitamin supplements) administered between Screening and the end of the Post-Treatment Period.

Allowed Concomitant Therapy

During the course of the study, the use of acute medications (plasma-derived or recombinant C1-INH concentrate, BK2-receptor antagonist, or kallikrein inhibitor) to treat angioedema attacks is allowed as medically indicated. Patients can be treated with on-demand therapy as determined by their treating physician.

All other stable medications (if not excluded below) are allowed, so long as the dose and type is not expected to change during the study.

Disallowed Concomitant Therapy

1. Chronic prophylaxis for angioedema attacks, except for a stable dose of androgens. Any use of lanadelumab will not be permitted.

NOTE: The use of acute medications (plasma-derived or recombinant C1-INH concentrate or BK2-receptor antagonist) to treat angioedema attacks is allowed as medically indicated.

2. ACE inhibitors or any estrogen-containing medications with systemic absorption (such as oral contraceptive or hormonal replacement therapy).
3. Any oligonucleotides (including small interfering RNA) other than ISIS 721744.
4. Plasmapheresis.
5. Any other investigational drug or device.

8.10.2. Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between Screening and the end of the Post-Treatment Period.

8.11. Treatment Compliance

Compliance with treatment dosing is to be monitored and recorded in the eCRF by Study Center staff.

9. SERIOUS AND NON-SERIOUS ADVERSE EVENT REPORTING

9.1. Sponsor Review of Safety Information

Safety information will be collected, reviewed, and evaluated by the Sponsor or designee in accordance with the applicable Ionis and/or designee Standard Operating Procedures throughout the conduct of the clinical study.

9.2. Regulatory Requirements

The Sponsor or designee is responsible for regulatory submissions and reporting to the Investigators of SAEs including SUSARs per the International Council for Harmonisation (ICH) guidelines E2A and ICH Good Clinical Practice (GCP). Country-specific regulatory requirements will be followed in accordance with local country regulations and guidelines.

Institutional Review Boards/IECs will be notified of any SAE according to applicable regulations. The DSMB will be notified of any SAE as specified in the DSMB Charter.

In addition to the Investigator's assessment of relatedness, the Sponsor or designee will evaluate the available information and perform an independent assessment of all reported SAEs and determine if there is a reasonable possibility that the Study Drug (ISIS 721744 or placebo) is causally related to a reported SAE. While the Sponsor may upgrade an Investigator's decision, it is not permissible to downgrade the Investigator's opinion for the purposes of determining whether the SAE meets the definition of a SUSAR.

Appropriate personnel at the Sponsor or designee will unblind SUSARs for the purpose of regulatory reporting. The Sponsor or designee will submit SUSARs to regulatory agencies in blinded or unblinded fashion according to local law. The Sponsor or designee will submit SUSARs to Investigators in a blinded fashion.

9.3. Definitions

9.3.1. Adverse Event

An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the AE is considered related to the medicinal (investigational) product.

An AE can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition)
- Recurrence of an intermittent medical condition (e.g., headache) not present at Baseline
- Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from Study Drug
- Events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)

9.3.2. Adverse Drug Reaction and Unexpected Suspected Adverse Drug Reaction

Adverse Drug Reaction

In the *pre-approval* clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not have been established, adverse drug reactions (ADRs) are defined as follows:

> All noxious and unintended responses to a medicinal product related to any dose should be considered ADRs.

The phrase “responses to a medicinal product” means that a causal relationship between the medicinal product and the AE has been determined by the Sponsor as at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Suspected Unexpected Adverse Drug Reaction

A suspected unexpected ADR is any ADR, the nature or severity of which is not consistent with the applicable product information, e.g., Investigator's Brochure for an unapproved medicinal (investigational) product.

A suspected adverse reaction implies a lesser degree of certainty about causality than an adverse reaction.

9.3.3. Serious Adverse Event

An SAE is any AE that, in the view of either the Investigator or Sponsor, meets any of the following criteria:

- Results in death
- Is life-threatening; that is, poses an immediate risk of death at the time of the event

  An AE or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator or Sponsor, its occurrence places the patient at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization

  Hospitalization is defined as an admission of greater than 24 hours to a medical facility and does not always qualify as an AE
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- Results in a congenital anomaly or birth defect in the offspring of the patient (whether the patient is male or female)
- Important medical events that may not result in death, are not life-threatening, or do not require hospitalization may also be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an AE (e.g., rated as mild, moderate, or severe according to National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE]); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each AE recorded on the eCRF.

9.3.4. Adverse Events of Special Interest

For the purpose of this study, severe reductions in platelet count < 50,000/mm^3 accompanied by a major bleeding (MB) event or clinically relevant non-major bleeding (CRNMB) event, or platelet count of < 25,000/mm^3 independent of a MB or CRNMB event, or any thrombotic episode are considered as AEs of special interest (AESIs) and are subject to 15-day expedited reporting by the Sponsor to the regulatory agencies.

9.4. Monitoring and Recording Adverse Events

Any pre-existing conditions or signs and/or symptoms present in a patient prior to the start of the study (i.e., before informed consent) should be recorded as Medical History and not recorded as

AEs unless the pre-existing condition worsened. The Investigator should always group signs and symptoms into a single term that constitutes a **single unifying diagnosis** if possible. Before a diagnosis is confirmed, all symptoms should be reported as separate AEs.

9.4.1. Serious Adverse Events

In the interest of patient safety, and in order to fulfill regulatory requirements**,** all SAEs (regardless of their relationship to Study Drug) should be reported to the Sponsor or designee within 24 hours of the Study Center's first knowledge of the event. The collection of SAEs will begin after the patient signs the ICF and will stop at the end of the patient's Post-Treatment Period, which is defined as completion of the Week 26/ET Visit. Serious adverse events should be reported using electronic SAE submission (via eDC) whenever possible. In situations where electronic SAE submission is unavailable, a paper Initial Serious Adverse Event Form should be completed and a copy should be faxed or emailed to the Sponsor or designee. The SAE reporting instructions, including the fax number and email address, can be found in the Investigator Site File for the study.

Detailed information should be actively sought and included as Follow-Up as soon as additional information becomes available. All SAEs will be followed until resolution. Serious adverse events that remain ongoing past the patient's last protocol-specified follow-up visit will be evaluated by the Investigator and Sponsor. If the Investigator and Sponsor agree that the patient's condition is unlikely to resolve, the Investigator and Sponsor will determine the follow-up requirement.

9.4.2. Non-Serious Adverse Events

The recording of non-serious AEs will begin after the patient signs the ICF and will stop at the end of the patient's Post-Treatment Period, which is defined as completion of the Week 26/ET Visit. The Investigator will monitor each patient closely and record all observed or volunteered AEs on the eCRF.

9.4.3. Evaluation of Adverse Events (Serious and Non-Serious)

The Investigator's opinion of the following should be documented on the eCRF:

9.4.3.1. Relationship to the Study Drug

The event's relationship to the Study Drug (ISIS 721744 or placebo) is characterized by 1 of the following:

- **Related:** There is clear evidence that the event is related to the use of Study Drug (ISIS 721744 or placebo), e.g., confirmation by positive re-challenge test
- **Possible:** The event cannot be explained by the patient's medical condition, concomitant therapy, or other causes, and there is a plausible temporal relationship between the event and Study Drug (ISIS 721744 or placebo) administration
- **Unlikely/Remote:** An event for which an alternative explanation is more likely (e.g., concomitant medications or ongoing medical conditions) or the temporal relationship to Study Drug (ISIS 721744 or placebo) administration and/or exposure suggests that a causal relationship is unlikely (for reporting purposes, Unlikely/Remote will be grouped together with Not Related)

- **Not Related:** The event can be readily explained by the patient's underlying medical condition, concomitant therapy, or other causes, and therefore, the Investigator believes no relationship exists between the event and Study Drug (ISIS 721744 or placebo)

9.4.3.2. Severity

The severity of AEs and SAEs relating to laboratory tests and AEs at the injection site will be graded based on criteria from the CTCAE Version 5.0, November 2017 (refer to Appendix D). Any AE not listed in Appendix D will be graded as follows:

- **Mild:** The event is easily tolerated by the patient and does not affect the patient's usual daily activities
- **Moderate:** The event causes the patient more discomfort and interrupts the patient's usual daily activities
- **Severe:** The event is incapacitating and causes considerable interference with the patient's usual daily activities

If the event is an SAE, then all applicable seriousness criteria must be indicated (criteria listed in Section 9.3.3).

9.4.3.3. Action Taken with Study Drug

Down-titration of Study Drug (ISIS 721744 or placebo) will not be allowed during the study.

Action taken with Study Drug (ISIS 721744 or placebo) due to an AE is characterized by 1 of the following:

- **None:** No changes made to Study Drug (ISIS 721744 or placebo) administration and dose
- **Not Applicable:** AE reported during the Screening Period prior to Study Drug (ISIS 721744 or placebo) administration
- **Permanently Discontinued:** Study Drug (ISIS 721744 or placebo) discontinued and not restarted
- **Temporarily Interrupted, Restarted – Same Dose:** Dosing and/or dosing frequency temporarily interrupted/changed or delayed due to the AE and restarted at the same dose

9.4.3.4. Treatment Given for Adverse Event

Any treatment (e.g., medications or procedures) given for the AE should be recorded on the eCRF. Treatment should also be recorded on the concomitant treatment or ancillary procedures eCRF, as appropriate.

9.4.3.5. Outcome of the Adverse Event

If the event is a non-serious AE, then the event's outcome is characterized by 1 of the following:

- **AE Persists:** Patient terminates from the study and the AE continues
- **Recovered:** Patient recovered completely from the AE
- **Became Serious:** The event became serious (the date that the event became serious should be recorded as the Resolution Date of that AE and the Onset Date of the corresponding SAE)
- **Change in Severity (if applicable):** AE severity changed

If the event is an SAE, then the event's outcome is characterized by 1 of the following:

- **Ongoing:** SAE continuing
- **Persists (as non-serious AE):** Patient has not fully recovered but the event no longer meets serious criteria and should be captured as an AE on the non-serious AE eCRF (the SAE resolution date should be entered as the date of onset of that AE)
- **Recovered:** Patient recovered completely from the SAE (the date of recovery should be entered as the SAE resolution date)
- **Recovered with Sequelae:** The signs/symptoms of the reported SAE have improved but not completely resolved, and a new baseline for the patient is established since full recovery is not expected
- **Fatal:** Patient died (the date of death should be entered as the SAE resolution date)
- **Unknown:** The outcome of the reported SAE is not available, e.g., patient is lost to follow-up

9.4.3.6. Follow-up of Adverse Event

Investigator Follow-up

During the Study Period, the Investigator should follow each AE until the event has resolved to baseline grade or better, the event is assessed as stable, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all SAEs considered to be related to Study Drug or related to study procedures until a final outcome can be reported.

Resolution of AE (with dates) should be documented on the eCRF and in the patient's medical record to facilitate source data verification.

Investigators should follow-up, or support the Sponsor's effort to follow up, with all pregnancies reported during the study from either the study patient or the female partner of the male study patient until pregnancy outcome is available.

Sponsor Follow-up

For SAEs and pregnancy cases in patients who have completed or terminated the study, the Sponsor or a designee should follow-up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, or autopsy reports) in order to perform an independent medical assessment of the reported case.

9.5. Procedures for Handling Special Situations

9.5.1. Abnormalities of Laboratory Tests

Clinically significant abnormal laboratory test results may, in the opinion of the Investigator, constitute or be associated with an AE. Examples of these include abnormal laboratory results that are associated with symptoms, or require treatment, e.g., bleeding due to thrombocytopenia, tetany due to hypocalcemia, or cardiac arrhythmias due to hyperkalemia. Whenever possible, the underlying diagnosis should be listed in preference to abnormal laboratory values as AEs. Clinically significant abnormalities will be monitored by the Investigator until the parameter returns to its baseline value or until agreement is reached between the Investigator and Sponsor Medical Monitor. Laboratory abnormalities deemed not clinically significant (NCS) by the Investigator should not be reported as AEs. Similarly, laboratory abnormalities reported as AEs by the Investigator should not be deemed NCS on the laboratory sheet.

The Investigator is responsible for reviewing and signing all laboratory reports. The signed clinical laboratory reports will serve as source documents and should include the Investigator's assessment of clinical significance of out of range/abnormal laboratory values.

9.5.2. Prescheduled or Elective Procedures or Routinely Scheduled Treatments

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered an SAE, even if the patient is hospitalized; the Study Center must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the patient's consent to participate in the study
- The condition that required the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the Investigator between the patient's consent to participate in the study and the timing of the procedure or treatment
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission

9.5.3. Dosing Errors

Study Drug (ISIS 721744 or placebo) dosing errors (including overdose, underdose, and administration error) should be documented as protocol deviations. A brief description should be provided in the deviation, including whether the patient was symptomatic (list symptoms) or asymptomatic, and the event accidental or intentional.

Dosing details should be captured on the Dosing eCRF. If the patient takes a dose of Study Drug (ISIS 721744 or placebo) that exceeds protocol specifications and the patient is symptomatic, then the symptom(s) should be documented as an AE and be reported per Section 9.4.

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of study treatment is not itself an AE, but it may result in an AE. All AEs associated with an overdose or incorrect administration of Study Drug should be recorded on the Adverse Event eCRF. If the associated AE fulfills seriousness criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event).

Should an overdose occur, the Investigator or designee should refer to the "Guidance for Investigator" section of the Investigator's Brochure and contact the Sponsor or designee within 24 hours.

9.5.4. Contraception and Pregnancy

Male patients and female patients of childbearing potential must continue to use highly effective contraception with their partners, or refrain from sexual activity, as described in Section 6.3.1.

If a patient becomes pregnant or a pregnancy is suspected, or if a male patient makes or believes that he has made someone pregnant during the study, then the Study Center staff must be informed immediately. An Initial Pregnancy Form should be submitted to the Sponsor or designee **within 24 hours** of first learning of the occurrence of pregnancy. Follow-up information including delivery or termination is reported by designating as 'Follow-up' on the Pregnancy Forms and reported within 24 hours.

Payment for all aspects of obstetrical care, child or related care will be the patient's responsibility.

Female patients: If a suspected pregnancy occurs while on the study (including the Post-Treatment Period), a pregnancy test will be performed. The patient with a confirmed pregnancy will be immediately withdrawn from treatment with Study Drug. However, the patient will be encouraged to complete the Post-Treatment Period of the study to the extent that study procedures do not interfere with the pregnancy. Regardless of continued study participation, the study physician will assist the patient in getting obstetrical care and the progress of the pregnancy will be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, the Study Center and Sponsor may require access to the mother and infant's medical records to obtain additional information relevant to the pregnancy progress and outcome. A longer follow-up may be required if a newborn child experiences a medical condition. Follow-up will be performed to the extent permitted by the applicable regulations and privacy considerations; e.g., pregnancy ICF may be required.

Male patients: The progress of the pregnancy of a male patient's partner should be followed until the outcome of the pregnancy is known (i.e., delivery, elective termination, or spontaneous abortion). If the pregnancy results in the birth of a child, the Study Center and Sponsor may follow-up with the mother and may request access to the mother and infant's medical records to obtain additional information relevant to the pregnancy progress and outcome. A longer follow-up may be required if a newborn child experiences a medical condition. Follow-up will be performed to the extent permitted by the applicable regulations and privacy considerations; e.g., partner ICF may be required.

10. STATISTICAL CONSIDERATIONS

The sections below indicate the overall structure and approach to the analysis of this study. A detailed SAP incorporating these sections below will be prepared separately. The SAP will outline all data handling conventions, including software, and specify additional statistical methods to be used for analysis. The study objectives and endpoints are listed in Sections 1.1 and 1.2, respectively.

10.1. Sample Size Considerations

The study will enroll a total of approximately 24 patients with HAE. Approximately 18 patients with HAE-1/HAE-2 are planned to be enrolled in Part A of the study and, in parallel, approximately 6 patients with HAE-nC1-INH are planned to be enrolled in Part B of the study. Due to the rarity of HAE-nC1-INH, enrollment in Part B may be ended early if Study Centers are unable to enroll sufficient patients; this will not impact completion of Part A. Patients with HAE-1/HAE-2 (Part A) will be randomized to SC injections of ISIS 721744 80 mg or placebo administered every 4 weeks in a 2:1 ratio (ISIS 721744:placebo), and patients with HAE-nC1-INH (Part B) will be administered open-label SC injections of ISIS 721744 80 mg every 4 weeks.

The sample size of 18 patients with HAE-1/HAE-2 (12 patients administered SC injections of ISIS 721744 80 mg and 6 patients administered placebo) is from clinical considerations for sufficient safety and tolerability evaluation. The primary endpoint is the time-normalized number of HAE attacks (per month) from Week 1 to Week 17. From historical data, the placebo group is estimated to have 6.8 HAE attacks per 4-month period. If the ISIS 721744 80 mg group is assumed to have 2.8 HAE attacks per 4-month period, then with a 0.05 significance level and Poisson model, the sample size of 18 patients will provide at least 90% power for the primary endpoint, considering a 10% missing data or dropout rate for both active treatment and placebo. There is no statistical rationale for the sample size of 6 patients with HAE-nC1-INH.

10.2. Populations

The Safety Population will include all enrolled patients who receive at least 1 dose of Study Drug (ISIS 721744 or placebo).

The Intent-to-Treat (ITT) Population will include all enrolled or randomized patients.

The Per-Protocol (PP) Population will include all patients in the ITT Population who are treated according to the protocol without any major deviations.

The PK Population will include all patients who are enrolled and receive at least 1 dose of Study Drug (ISIS 721744 or placebo) and have at least 1 evaluable PK sample.

10.3. Definition of Baseline

For platelets, Baseline will be defined as the average of all non-missing pre-dose assessments.

For other assessments, if there are 2 or more pre-dose values available, Baseline will be defined as the average of the pre-dose Study Day 1 value and the last pre-dose value prior to Study Day 1. If there is only 1 pre-dose measurement available, then it will be assigned as Baseline.

10.4. Data and Safety Monitoring Board

An independent DSMB will be established prior to the initiation of the study. The DSMB will be responsible for monitoring the overall safe conduct of the study. Based on its ongoing assessment of the safety and tolerability of ISIS 721744, the DSMB will provide recommendations to the Sponsor for modifying, stopping, or continuing the study as planned.

Details on the safety assessments, frequency of review, meeting schedules and controlled access to unblinded data are outlined in the DSMB Charter and SAP.

10.5. Interim Analysis

No interim analysis is planned for this study.

10.6. Planned Methods of Analysis

10.6.1. Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized using descriptive statistics by treatment group. Patient disposition will be summarized by treatment group. All patients enrolled will be included in a summary of patient disposition.

10.6.2. Safety Analysis

The Safety Population will be used for all safety analyses.

The safety and tolerability of ISIS 721744 will be assessed by determining the number, type, severity, and dose-relationship of AEs; vital signs; ECGs; and clinical laboratory parameters. Safety results in patients dosed with ISIS 721744 will be compared to safety results in patients dosed with placebo.

Treatment duration and amount of Study Drug (ISIS 721744 or placebo) received will be summarized by treatment group. Patient incidence rates of all AEs will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA™) system organ class and by MedDRA preferred term. Tables and/or narratives of treatment-emergent deaths and serious and significant AEs, including early withdrawals due to AEs, will also be provided.

All TEAEs, all TEAEs potentially related to Study Drug, all treatment-emergent SAEs, and all treatment-emergent SAEs potentially related to Study Drug (ISIS 721744 or placebo) will be summarized.

Laboratory tests to ensure patient safety, including chemistry panel, complete blood count with differential, coagulation panel, and complement, will be summarized by study visit for each treatment group. These safety variables will also be presented as change and percent change from Baseline over time after Study Drug (ISIS 721744 or placebo) administration, as appropriate.

Vital sign and ECG measures will be tabulated by treatment group. In addition, the number of patients who experience abnormalities in clinical laboratory evaluations will be summarized by treatment group.

10.6.3. Efficacy Analysis

The ITT Population will be used for all efficacy analyses. The PP Population will be used for a sensitivity analysis to assess robustness of the efficacy analysis results.

The definition of an HAE attack, including discrete attacks, is provided in Section 6.2.1.

10.6.3.1. Primary Efficacy Analysis

The primary endpoint is the time-normalized number of HAE attacks (per month) from Week 1 to Week 17.

The Part A data will be analyzed using a Poisson regression model with treatment group as a fixed effect and the number of baseline HAE attacks as a covariate, and the logarithm of exposure in month will be used as the offset.

The least-squares means, standard errors, and the 2-tailed 95% confidence intervals for the treatment group and placebo group will be presented.

The Part B data will be summarized using descriptive statistics.

10.6.3.2. Secondary Efficacy Analysis

The secondary endpoints include the time-normalized number of HAE attacks (per month) from Week 5 to Week 17; the time-normalized number of moderate or severe HAE attacks (per month) from Week 5 to Week 17; the number of patients with a clinical response (defined as a $\geq 50\%$, $\geq 70\%$, or $\geq 90\%$ reduction from Baseline in HAE attack rate) by Week 17; the number of HAE attacks requiring acute therapy from Week 5 to Week 17; cHK levels at Weeks 9 and 17; PKK activity at Weeks 9 and 17; consumption of on-demand medication at Weeks 9 and 17; and AE-QoL questionnaire score at Weeks 9 and 17.

For Part A, the time-normalized number of HAE attacks (per month) from Week 5 to Week 17 and the time-normalized number of moderate or severe HAE attacks (per month) from Week 5 to Week 17 will be analyzed in a similar way to the primary efficacy endpoint.

Continuous variables will be summarized by descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) by treatment group. Continuous variables will also be analyzed using analysis of covariance or analysis of variance. The least-squares means, standard errors, and the 2-tailed 95% confidence intervals for the treatment group and placebo group will be presented.

Categorical variables will be summarized by frequency and percentage for the treatment group and placebo group. Categorical variables will be analyzed using a Pearson's Chi-square test or Cochran-Mantel-Haenszel test.

The Part B data will be summarized using descriptive statistics.

10.6.3.3. Exploratory Efficacy Analysis

Exploratory efficacy endpoints include the number of HAE attack-free patients by Week 17 and potential exposure response analysis using relevant exposure parameters and biomarkers. All exploratory efficacy endpoints will be analyzed using the same methods as described for the secondary efficacy endpoints.

10.6.4. Pharmacokinetic Analysis

The plasma PK of ISIS 721744 will be assessed following SC administration. For all patients, Pre-Dose (trough) and Post-Treatment plasma ISIS 721744 concentrations will be determined and summarized using descriptive statistics. Plasma terminal elimination half-life will also be

calculated using the Post-Treatment follow up ISIS 721744 plasma concentrations, if data permits. For patients in the PK sub group, non-compartmental PK analysis of ISIS 721744 will be carried out on each individual patient dataset.

Pharmacokinetic parameters include (but are not limited to) the following: C_{max}, T_{max}, AUC, and $t_{½}$. Other plasma PK parameters, as appropriate, may be determined or calculated at the discretion of the PK scientist.

Metabolite identification and profiling may be conducted on select plasma samples.

Plasma PK parameters will be summarized using descriptive statistics. Additional details regarding the PK analysis along with immunogenicity (IM) analysis will be described in the SAP.

Analysis of potential exposure-response relationship between biomarkers and PK measures may also be explored.

Population PK and PK/PD analyses may be performed using PK data from this study, and/or combined with other ISIS 721744 clinical PK/PD data later in the development timeline.

11. INVESTIGATOR'S REGULATORY OBLIGATIONS

11.1. Informed Consent

The written informed consent document should be prepared in the language(s) of the potential patient population, based on an English version provided by the Sponsor or designee.

Before a patient's participation in the study, the Investigator is responsible for obtaining written informed consent from the patient after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures or any Study Drug (ISIS 721744 or placebo) are administered. The patient must be given sufficient time to consider whether to participate in the study.

The acquisition of informed consent and the patient's agreement or refusal to notify his/her primary care physician should be documented in the patient's medical records and the ICF should be signed and personally dated by the patient and by the person who conducted the informed consent discussion (not necessarily an Investigator). The original signed ICF should be retained in the Study Master File and in any other locations required by institutional policy, and a copy of the signed consent form should be provided to the patient.

11.2. Ethical Conduct of the Study

All applicable regulations and guidelines of current GCP as well as the demands of national drug and data protection laws and other applicable regulatory requirements must be followed.

11.3. Independent Ethics Committee/Institutional Review Board

A copy of the protocol, proposed ICF, other written patient information, and any proposed advertising material must be submitted to the IEC/IRB for written approval. A copy of the written approval of the protocol and ICF must be received by the Sponsor or designee before

recruitment of patients into the study and shipment of Study Drug. A copy of the written approval of any other items/materials that must be approved by the Study Center or IEC/IRB must also be received by the Sponsor or designee before recruitment of patients into the study and shipment of Study Drug. The Investigator's Brochure must be submitted to the IEC/IRB for acknowledgement.

The Investigator must submit to and, where necessary, obtain approval from the IEC/IRB, for all subsequent protocol amendments and changes to the informed consent document. The Investigator should notify the IEC/IRB of deviations from the protocol in accordance with ICH GCP. The Investigator should also notify the IEC/IRB of SAEs occurring at the Study Center and other AE reports received from the Sponsor or designee, in accordance with local procedures.

The Investigator will be responsible for obtaining annual IEC/IRB approval/renewal throughout the duration of the study. Copies of the Investigator's reports, all IEC/IRB submissions and the IEC/IRB continuance of approval must be sent to the Sponsor or designee.

11.4. Patient Confidentiality

The Investigator must ensure that the patient's confidentiality is maintained. On the case report forms or other documents submitted to the Sponsor or designee, patients should be identified by initials (if permitted by local law) and a patient identification number only. Documents that are not for submission to the Sponsor or designee (e.g., signed ICFs) should be kept in strict confidence by the Investigator.

In compliance with federal and local regulations/ICH GCP Guidelines, it is required that the Investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IEC/IRB direct access to review the patient's original medical records for verification of study-related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The Investigator is obligated to inform and obtain the consent of the patient to permit named representatives to have access to his/her study-related records without violating the confidentiality of the patient.

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1. Protocol Amendments

Protocol amendments must be made only with the prior approval of the Sponsor or designee. Agreement from the Investigator must be obtained for all protocol amendments and amendments to the informed consent document. The regulatory authority and IEC/IRB must be informed of all amendments and give approval for any amendments likely to affect the safety of the patients or the conduct of the study. The Investigator **must** send a copy of the approval letter from the IEC/IRB to the Sponsor or designee.

12.2. Study Termination

The Sponsor or designee reserves the right to terminate the study. The Investigator reserves the right to terminate their participation in the study, according to the terms of the Study Center contract. The Investigator/Sponsor or designee should notify the IEC/IRB in writing of the study's completion or ET and send a copy of the notification to the Sponsor or designee.

12.3. Study Documentation and Storage

An eCRF utilizing an Electronic Data Capture application will be used for this study.

The Investigator should ensure that all appropriately qualified persons to whom he/she has delegated study duties are recorded on a Sponsor-approved Delegation of Site Responsibilities Form.

Source documents are original documents, data, and records from which the patient's case report form data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, imaging, and correspondence. In this study, eCRFs may not be used as source documents.

The Investigator and Study Center staff are responsible for maintaining a comprehensive and centralized filing system of all study-related (essential) documentation in accordance with ICH GCP, suitable for inspection at any time by representatives from the Sponsor or designee and/or applicable regulatory authorities. Elements should include the following:

- Patient files containing completed case report forms, informed consents, and supporting copies of source documentation
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of pre-study documentation and all correspondence to and from the IEC/IRB and the Sponsor or designee
- If drug supplies are maintained at the Study Center, proof of receipt, Study Drug Product Accountability Record, Return of Study Drug Product for Destruction, final Study Drug product reconciliation, and all drug-related correspondence

In addition, all original source documents supporting entries in the case report forms must be maintained and be readily available.

No study document should be destroyed without prior written agreement between the Sponsor or designee and the Investigator. Should the Investigator wish to assign the study records to another party or move them to another location, he/she must notify the Sponsor or designee.

12.4. Study Monitoring

The Sponsor representative and regulatory authority inspectors are responsible for contacting and visiting the Investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the study (e.g., case report forms and other pertinent data) provided that patient confidentiality is respected.

The Sponsor monitor or designee is responsible for inspecting the case report forms at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and

consistency of the data; and adherence to local regulations on the conduct of clinical research. The monitor should have access to patient medical records and other study-related records needed to verify the entries on the case report forms.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing case report forms, are resolved.

In accordance with ICH GCP and the Sponsor's audit plans, this study may be selected for audit by representatives from the Sponsor's Clinical Quality Assurance Department (or designees). Inspection of Study Center facilities (e.g., pharmacy, drug storage areas, laboratories) and review of study-related records will occur to evaluate the study conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

To ensure the quality of clinical data a clinical data management review will be performed on patient data received by the Sponsor or designee. During this review, patient data will be checked for consistency, omissions, and any apparent discrepancies. In addition, the data will be reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or Study Center notifications will be sent to the Study Center for completion and return to Sponsor or designee.

The Principal Investigator will sign and date the indicated places on the case report form. These signatures will indicate that the Principal Investigator inspected or reviewed the data on the case report form, the data queries, and the Study Center notifications, and agrees with the content.

12.5. Language

Case report forms must be completed in English. Generic names and trade names are acceptable for concomitant medications. Combination medications should be recorded using their trade name.

All written information and other material to be used by patients and investigative staff must use vocabulary and language that are clearly understood.

12.6. Compensation for Injury

The Sponsor maintains appropriate insurance coverage for clinical studies and will follow applicable local compensation laws. Patients will be treated and/or compensated for any study-related illness/injury in accordance with the information provided in the Compensation for Injury section of the ICF.

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14. APPENDICES

APPENDIX A. SCHEDULE OF PROCEDURES

Appendix A. Schedule of Procedures

	Screening[1]	Treatment Period (12 Weeks)					Post-Treatment Period[16] (13 Weeks)		
Study Week/Day	**Weeks -8 to -1 Days -56 to -1**	**Week 1 Day 1**	**Week 3 Day 15[17]**	**Week 5 Day 29[17]**	**Week 9 Day 57[17]**	**Week 13 Day 85[17]**	**Week 17 Day 113 or ET[17]**	**Week 21 Day 141[17]**	**Week 26 Day 176[17]**
Visit Window (Days)	**± 0**	**± 0**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 3**
Informed Consent	X								
Inclusion/Exclusion	X								
Demographics and Medical History (including detailed HAE history)	X								
Prior/Concomitant Medications (including HAE treatment)	X	X	X	X	X	X	X	X	X
Body Weight and Height[2]	X	X	X	X	X	X	X	X	X
Physical Examination	X	X		X	X	X	X	X	X
Vital Signs[3]	X	X	X	X	X	X	X	X	X
HIV, Hepatitis B, and Hepatitis C	X								
FSH[4]	X								
Pregnancy Test[5]	X	X		X	X	X	X	X	X
Clinical Laboratory Parameters (chemistry, hematology, complement, and coagulation)[6, 7]	X	X	X	X	X	X	X	X	X

Appendix A. Schedule of Procedures Continued

	Screening[1]	Treatment Period (12 Weeks)					Post-Treatment Period[16] (13 Weeks)		
Study Week/Day	**Weeks -8 to -1 Days -56 to -1**	**Week 1 Day 1**	**Week 3 Day 15[17]**	**Week 5 Day 29[17]**	**Week 9 Day 57[17]**	**Week 13 Day 85[17]**	**Week 17 Day 113 or ET[17]**	**Week 21 Day 141[17]**	**Week 26 Day 176[17]**
Visit Window (Days)	**± 0**	**± 0**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 3**
Urinalysis	X	X	X	X	X	X	X	X	X
Threshold-Stimulated Kallikrein Activity (if applicable)[8]	X								
Genetic Diagnostic Testing (if applicable)[9]	X								
AE-QoL	X	X			X		X		X
Angioedema Activity Score[10]	X	X	X	X	X	X	X	X	X
HAE Attack Assessment (including on-demand treatment)[11, 12]	X	X	X	X	X	X	X	X	X
12-Lead ECG	X	X			X		X		X
Randomization[13]		X							
Study Drug Administration (ISIS 721744 or placebo)		X		X	X	X			
Adverse Events	X	X	X	X	X	X	X	X	X
Immunogenicity Testing		X[a]	X	X[a]	X[a]		X		X

Appendix A. Schedule of Procedures Continued

	Screening[1]	Treatment Period (12 Weeks)					Post-Treatment Period[16] (13 Weeks)		
Study Week/Day	**Weeks -8 to -1 Days -56 to -1**	**Week 1 Day 1**	**Week 3 Day 15[17]**	**Week 5 Day 29[17]**	**Week 9 Day 57[17]**	**Week 13 Day 85[17]**	**Week 17 Day 113 or ET[17]**	**Week 21 Day 141[17]**	**Week 26 Day 176[17]**
Visit Window (Days)	**± 0**	**± 0**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 2**	**± 3**
PK Blood Sampling[14]		X[b]	X	X[a]	X[a]	X[b]	X	X	X
PD Blood Sampling[15]	X	X[a]	X	X[a]	X[a]	X[a]	X	X	X
Inflammatory Panel	X	X[a]	X	X[a]	X[a]	X[a]	X	X	X

Note: When multiple procedures are scheduled at the same visit, clinical assessments and procedures should be performed prior to Study Drug administration, unless otherwise indicated, and should proceed in the following order: vital signs, physical examinations, patient-reported outcomes (such as the AAS and the AE-QoL questionnaire), ECGs, and collection of blood and/or urine for laboratory assessments.

1 The Screening Period is up to 8 weeks in duration. A patient may be randomized after fewer than 8 weeks of Screening if the patient experiences ≥ 2 HAE attacks in less than 8 weeks and has completed all other screening activities and has met all other eligibility requirements.

2 Height will be measured at Screening only.

3 Vital signs will include blood pressure, heart rate, respiratory rate, and body temperature and should be taken after sitting for at least 5 min.

4 For confirmation of menopause at Screening per inclusion criteria.

5 Only for women who are not surgically sterile or post-menopausal. A serum pregnancy test will be performed during Screening and urine pregnancy tests will be performed at all other study visits.

6 If the platelet value, serum creatinine, or liver enzyme tests are uninterpretable (e.g., due to clumping, hemolysis, or quantity not sufficient) or missing, a repeat blood specimen should be re-drawn as soon as possible (ideally within 7 days).

7 For a complete list of laboratory analytes, refer to Appendix B.

8 Will be assessed only in patients who have HAE-nC1-INH without a factor XII mutation or the plasminogen or angiopoietin-1 mutation.

9 Will be performed only for patients who do not have HAE genetic diagnostic testing results prior to Screening.

10 The AAS questionnaire will be completed by patients on a daily basis (minimum of 4 daily assessments per week) for the duration of the study. Patients will be instructed on the use of the AAS during Screening and will record their HAE attacks using the AAS throughout the Screening Period (daily during up to 8 consecutive weeks) to confirm study eligibility; patients are required to experience at least 2 HAE attacks (assessed by the AAS and confirmed by the Investigator) during the Screening Period to be eligible for enrollment. If a patient experiences a third attack, the patient should be randomized as soon as possible, assuming all other screening activities have been completed and the patient meets all other eligibility requirements; in such cases, the Screening Period may be shorter than 8 weeks. Enrolled patients will continue to record HAE attacks using the AAS throughout the Treatment and Post-Treatment Periods.

Legend Continued

[11] Historical HAE attack information will be collected at Screening. During the study, patients will be instructed to report details of any HAE attack to the study site within 72 hours of the onset of the attack. Throughout the Screening, Treatment, and Post-Treatment Periods, site personnel will contact the patient once a week (at approximately 7 days after the last contact with the patient) in order to inquire about any attack that may have occurred. In addition, during study visits, site personnel will inquire about any new HAE attack information that was not provided through patient contact with the site.

[12] The following details relating to the localization, severity, and course of all HAE attacks that occured since the previous visit will be collected: date/time of symptom onset; description of symptoms; location of symptoms (peripheral angioedema, abdominal angioedema, or laryngeal angioedema); impact of HAE attack on activity level; HAE attack severity (mild, moderate, or severe); need for assistance, medical intervention, emergency room visit, or hospitalization; medications to treat the attack; HAE attack course, including if the HAE attack(s) in question was a typical attack for the patient, or if there was an alternative diagnosis; and date/time symptoms resolved. The number of HAE attacks that required on-demand treatment, and the frequency and dose of on-demand treatment, will also be recorded.

[13] After all screening assessments have been completed and the Investigator has verified that the patient is eligible.

[14] Refer to Appendix C for the PK Sampling Schedule.

[15] To be collected at each visit to assess plasma PKK, plasma proenzyme activation, and cHK levels.

[16] Patients who complete Study Visit Week 17, and meet eligibility requirements, may start the Treatment Period in the ISIS 721744-CS3 OLE study anytime after the Week 17 visit and discontinue participation in the CS2 Post-Treatment Evaluation Period.

[17] Assessments and procedures may be conducted by either a Home Healthcare professional (if available), or the Study Center as arranged by the Study Center personnel. Physical Exam will be labeled Body Assessment if conducted by Home Healthcare professional. Study Drug administration by Home Healthcare professional may be done only after study drug for home use is available.

Time (time is in reference to Study Drug administration [ISIS 721744 or placebo]):

[a] Pre-dose.

[b] Pre-dose, 1, 2, 4, and 6 hours post-dose (PK Subgroup) or Pre-dose and 2-hours post-dose.

APPENDIX B. LIST OF LABORATORY ANALYTES

Appendix B List of Laboratory Analytes

Based on emerging data from this or future studies, additional tests not listed below may be performed on stored samples to better characterize the profile of ISIS 721744 or other similar oligonucleotides.

Chemistry Panel

- Sodium
- Potassium
- Chloride
- Bicarbonate
- Total protein
- Albumin
- Calcium
- Magnesium
- Phosphorus
- Glucose
- BUN
- Creatinine
- Cholesterol
- Uric Acid
- Total bilirubin
- Direct (conjugated) bilirubin
- Indirect (unconjugated) bilirubin
- ALT
- AST
- Alkaline phosphatase
- Creatine kinase
- GGT

Screening Tests

- Hepatitis B surface antigen
- Hepatitis C antibody
- HIV antibody
- FSH (for confirmation of menopause at Screening per inclusion criteria)
- Serum βhCG (only women who are not surgically sterile or post-menopausal)

Coagulation

- aPTT (sec)
- PT (sec)
- INR
- Plasmin-antiplasmin complexes
- D-dimer

Complement

- C5a
- Bb
- C4 split products
- C4

Pharmacodynamics Panel

- Plasma PKK
- Plasma proenzyme activation
- cHK

Hematology

- Red blood cells
- Hemoglobin
- Hematocrit
- MCV, MCH, MCHC
- Platelets
- White blood cells (WBC)
- WBC Differential (% and absolute)
- Neutrophils
- Eosinophils
- Basophils
- Lymphocytes
- Monocytes

Pharmacokinetics[1]

- ISIS 721744 concentration in plasma

Immunogenicity

- Anti-ISIS 721744 antibodies

Inflammatory

- hs-CRP

Urinalysis

- Color
- Appearance
- Specific gravity
- pH
- Protein/creatinine ratio
- Protein
- Blood
- Ketones
- Urobilinogen
- Glucose
- Bilirubin
- Leukocyte esterase
- Nitrate
- eGFR
- Microscopic examination[2]

[1] Plasma PK samples may also be used for profiling of drug binding proteins, bioanalytical method validation purposes, stability assessments, metabolite assessments, or to assess other actions of ISIS 721744 with plasma constituents.

[2] Will be performed on abnormal findings unless otherwise specified.

APPENDIX C. PHARMACOKINETIC SAMPLING SCHEDULE

Appendix C Pharmacokinetic Sampling Schedule

PK samples on Day 1 and Day 85 will be collected pre-dose, and 1, 2, 4, and 6 hours post-dose in PK subgroup only (approximately 6 patients) while pre-dose and 2 hours post-dose samples on Day 1 and Day 85 will be collected for all other patients. The rest of the sampling schedule will be the same for both sets of pateints (see table below):

Pharmacokinetic Sampling Schedule

	Day 1	**Day 15**	**Day 29**	**Day 57**	**Day 85**	**Day 113**	**Day 141**	**Day 176**
PK Subgroup	Blood: Pre-dose, 1, 2, 4, and 6 hours post-dose	Blood: Anytime	Blood: Pre-dose	Blood: Pre-dose	Blood: Pre-dose, 1, 2, 4, and 6 hours post-dose	Blood: Anytime	Blood: Anytime	Blood: Anytime
All Patients	Blood: Pre-dose, 2 hours post-dose	Blood Anytime	Blood: Pre-dose	Blood: Pre-dose	Blood: Pre-dose, 2 hours post-dose	Blood Anytime	Blood Anytime	Blood Anytime

APPENDIX D. GRADING SCALE FOR ADVERSE EVENTS RELATING TO LABORATORY ABNORMALITIES

Appendix D Grading Scale for Adverse Events Relating to Laboratory Abnormalities

The following grading recommendations for adverse events relating to lab test abnormalities and adverse events at the injection site are based on the CTCAE Version 5.0, November 2017 with modifications outlined in the footnotes below.

Adverse Event	Mild	Moderate	Severe
Hematology			
aPTT prolonged	>ULN - 1.5 x ULN	>1.5 - 2.5 x ULN	>2.5 x ULN; bleeding
Eosinophils increased[1]	>ULN and >Baseline	-	Steroids Initiated
Fibrinogen decreased	<1.0 - 0.75 x LLN; if abnormal, <25% decrease from baseline	<0.75 - 0.5 x LLN; if abnormal, 25 - <50% decrease from baseline	<0.5 x LLN; if abnormal, ≥50% decrease from baseline
Hemoglobin decreased (Anemia)	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated
Hemoglobin increased**	Increase in >0 - 2 g/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 g/dL above ULN or above baseline if baseline is above ULN	Increase in >4 g/dL above ULN or above baseline if baseline is above ULN
INR increased	>1.2 - 1.5; >1 - 1.5 times above baseline if on anticoagulation	>1.5 - 2.5; >1.5 - 2.5 x baseline if on anticoagulation; monitoring only indicated	>2.5; >2.5 x baseline if on anticoagulation; dose adjustment indicated
Lymphocyte count decreased	<LLN - 800/mm^3; <LLN - 0.8 x 10^9/L	<800 - 500/mm^3; <0.8 - 0.5 x 10^9 /L	<500 /mm^3; <0.5 x 10^9 /L
Lymphocyte count increased	-	>4000/mm^3 - 20,000/mm^3	>20,000/mm^3
Neutrophil count decreased	<LLN - 1500/mm^3; <LLN - 1.5 x 10^9 /L	<1500 - 1000/mm^3; <1.5 - 1.0 x 10^9 /L	<1000/mm^3; <1.0 x 10^9 /L
Platelet count decreased	<LLN - 75,000/mm^3; <LLN - 75.0 x 10^9 /L	<75,000 - 50,000/mm^3; <75.0 - 50.0 x 10^9 /L	<50,000/mm^3; <50.0 x 10^9 /L
White blood cell decreased	<LLN - 3000/mm^3; <LLN - 3.0 x 10^9 /L	<3000 - 2000/mm^3; <3.0 - 2.0 x 10^9 /L	<2000/mm^3; <2.0 x 10^9 /L
Chemistry			
Acidosis	pH <normal, but >=7.3	-	pH <7.3
Alanine aminotransferase increased	>ULN - 3.0 x ULN if baseline normal 1.5 - 3.0 x baseline if baseline abnormal	>3.0 - 5.0 x ULN if baseline normal >3.0 - 5.0 x baseline if baseline abnormal	>5.0 x ULN if baseline normal >5.0 x baseline if baseline abnormal
Alkaline phosphatase increased	>ULN - 2.5 x ULN if baseline normal 2.0 - 2.5 x baseline if baseline abnormal	>2.5 - 5.0 x ULN if baseline normal >2.5 - 5.0 x baseline if baseline abnormal	>5.0 x ULN if baseline normal >5.0 x baseline if baseline was abnormal
Alkalosis	pH >normal, but ≤7.5	-	pH >7.5
Aspartate aminotransferase increased	>ULN - 3.0 x ULN if baseline normal 1.5 - 3.0 x baseline if baseline abnormal	>3.0 - 5.0 x ULN if baseline normal >3.0 - 5.0 x baseline if baseline abnormal	>5.0 x ULN if baseline normal >5.0 x baseline if baseline abnormal
Blood bilirubin increased	>ULN - 1.5 x ULN if baseline normal >1.0 - 1.5 x baseline if baseline abnormal	>1.5 - 3.0 x ULN if baseline normal >1.5 - 3.0 x baseline if baseline abnormal	>3.0 x ULN if baseline normal >3.0 x baseline if baseline abnormal
Cardiac troponin I increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer

Adverse Event	Mild	Moderate	Severe
Cardiac troponin T increased	Levels above the upper limit of normal and below the level of myocardial infarction as defined by the manufacturer	-	Levels consistent with myocardial infarction as defined by the manufacturer
CD4 lymphocytes decreased	<LLN - 500/mm^3; <LLN - 0.5 x 10^9 /L	<500 - 200/mm^3; <0.5 - 0.2 x 10^9 /L	<200/mm^3; <0.2 x 10^9 /L
CPK increased*	>ULN - <6 ULN	6 - 10 x ULN	>10 x ULN
Creatinine increased**	>ULN - 1.5 x ULN if baseline normal > 1.0 - 1.5 x baseline if baseline abnormal	>1.5 - 3.0 x ULN if baseline normal >1.5 - 3.0 x baseline if baseline abnormal	>3.0 x ULN if baseline normal >3.0 x baseline if baseline abnormal
GGT increased	>ULN - 2.5 x ULN if baseline normal 2.0 - 2.5 x baseline if baseline abnormal	>2.5 - 5.0 x ULN if baseline normal >2.5 - 5.0 x baseline if baseline abnormal	>5.0 x ULN if baseline normal >5.0 x baseline if baseline abnormal
Hypercalcemia	Corrected serum calcium of >ULN - 11.5 mg/dL; >ULN - 2.9 mmol/L; Ionized calcium >ULN - 1.5 mmol/L	Corrected serum calcium of >11.5 - 12.5 mg/dL; >2.9 - 3.1 mmol/L; Ionized calcium >1.5 - 1.6 mmol/L; symptomatic	Corrected serum calcium of >12.5 mg/dL; >3.1 mmol/L; Ionized calcium >1.6 mmol/L; hospitalization indicated
Hyperglycemia††	Fasting glucose value ≥126 mg/dL (7.0 mmol/L)	Change in daily management to maintain fasting blood glucose <126 mg/dL (7.0 mmol/L); e.g. addition of oral antiglycemic agent; workup for diabetes	Insulin therapy initiated; hospitalization indicated
Hyperkalemia	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L; intervention initiated	>6.0; hospitalization indicated
Hypermagnesemia	>ULN - 3.0 mg/dL; >ULN - 1.23 mmol/L	-	>3.0 mg/dL; >1.23 mmol/L
Hypernatremia	>ULN - 150 mmol/L	>150 - 155 mmol/L; intervention initiated	>155 mmol/L; hospitalization indicated
Hyperphosphatemia	Laboratory finding only and intervention not indicated	Noninvasive intervention indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated
Hyperuricemia	>ULN without physiologic consequences	-	>ULN with physiologic consequences
Hypoalbuminemia	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L
Hypocalcemia	Corrected serum calcium of <LLN - 8.0 mg/dL; <LLN - 2.0 mmol/L; Ionized calcium <LLN - 1.0 mmol/L	Corrected serum calcium of <8.0 - 7.0 mg/dL; <2.0 - 1.75 mmol/L; Ionized calcium <1.0 - 0.9 mmol/L; symptomatic	Corrected serum calcium of <7.0 mg/dL; <1.75 mmol/L; Ionized calcium <0.9 mmol/L; hospitalization indicated
Hypoglycemia‡	≥54 mg/dL - <70 mg/dL ≥3.0 mmol/L - <3.9 mmol/L	<54 mg/dL (3.0 mmol/L) AND no assistance required to actively administer carbohydrates, glucagon, or take other corrective actions	Requires assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions
Hypokalemia	<LLN - 3.0 mmol/L	symptomatic with <LLN - 3.0 mmol/L; intervention indicated	<3.0 mmol/L; hospitalization indicated
Hypomagnesemia	<LLN - 1.2 mg/dL; <LLN - 0.5 mmol/L	<1.2 - 0.9 mg/dL; <0.5 - 0.4 mmol/L	<0.9 mg/dL; <0.4 mmol/L
Hyponatremia	<LLN - 130 mmol/L	125-129 mmol/L and asymptomatic	125-129 mmol/L symptomatic; 120-124 mmol/L regardless of symptoms
Hypophosphatemia	Laboratory finding only and intervention not indicated	Oral replacement therapy indicated	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated
Lipase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; >2.0 - 5.0 x ULN and asymptomatic	>2.0 x ULN with signs or symptoms
Serum amylase increased	>ULN - 1.5 x ULN	>1.5 - 2.0 x ULN; >2.0 - 5.0 x ULN and asymptomatic	>2.0 x ULN with signs or symptoms

Adverse Event	Mild	Moderate	Severe
Urine			
Proteinuria Adults	1+ proteinuria; urinary protein ≥ULN - <1.0 g/24 hrs	2+ and 3+ proteinuria; urinary protein 1.0 - 3.4 g/24 hrs;	4+ proteinuria; Urinary protein ≥3.5 g/24 hrs;
Children	-	Urine P/C (Protein/Creatinine) ratio 0.5 - 1.9	Urine P/C >1.9
Hematuria	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	Symptomatic; urinary catheter or bladder irrigation indicated	Gross hematuria; transfusion, IV medications or hospitalization indicated; elective invasive intervention indicated
Adverse Events at the Injection Site			
Adverse events at the injection site**	An event at the injection site (e.g. erythema, tenderness, itching) that is easily tolerated by the subject and does not affect the subject's usual daily activities	- Persistent (>24 hours) pain, phlebitis or edema; OR - Lipodystrophy, hair growth or alopecia, OR - Prolonged (>1 month) hypo/hyperpigmentation	- Ulceration or necrosis; severe tissue damage; operative intervention indicated, OR - Any event at the injection site that is incapacitating

†Grading for this parameter is derived from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials, Sept 2007

*Grading for this parameter is derived from the Division of AIDS (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events Version 2.0, Nov 2014

††Modified for consistency with ADA "Standards of Medical Care in Diabetes - 2018" Diabetes Care 2018;41(Suppl. 1):S13–S27. https://doi.org/10.2337/dc18-S002

‡Modified for consistency with ADA "Glycemic Targets: Standards of Medical Care in Diabetes - 2018", Diabetes Care 2018;41(Suppl. 1):S55–S64. https://doi.org/10.2337/dc18-S006

**Adapted from the original CTCAE V5.0 scale

PROTOCOL AMENDMENTS

Protocol Number: ISIS 721744-CS2

Protocol Title: A Randomized, Double-Blind, Placebo-Controlled, Phase 2a Study to Assess the Clinical Efficacy of ISIS 721744, a Second-Generation Ligand-Conjugated Antisense Inhibitor of Prekallikrein, in Patients With Hereditary Angioedema

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A list of changes to the protocol are below:

Amendment	Description of Changes	Dates
Amendment 1	The purpose of this protocol amendment is to implement the following modifications to Protocol ISIS 721744-CS2 date 03 May 2019: 1. Specify a minimal compliance level in the inclusion criteria for completion of the Angioedema Activity Score, during the screening period, as a requirement prior to randomization to treatment in Part A, or initiation of treatment in Part B, of the study 2. Broaden the exclusion criteria to include: elevated PTT, history of coagulopathy or bleeding diathesis, and renal and hepatic diseases 3. Modify the exclusion criteria to allow for participants that test positive for hepatitis B or C enzyme but are non-reactive 4. Provide the definition of an HAE attack and delineate how discrete attacks will be counted 5. Designate adverse events of special interest (AESIs) 6. Add anti-drug antibody testing at Day 15 and Day 29 visits, and remove the requirement for a physical examination from the day 15 visit, in the Schedule of Procedures Minor changes have been made throughout the protocol to correct errors and/or to improve the overall clarity of the original	21 October 2019
Amendment 2	The purpose of this protocol amendment is to implement the following modifications to Protocol ISIS 721744-CS2, Amendment 1, dated 21 October 2019:	29 January 2019

	1. To update the established mutations in the plasminogen and angiopoietin genes from the legacy description to the Human Genome Variation Society (HGVS) description in the diagnostic report. The plasminogen gene was changed from c.9886A>G to 988A>G and the angiopoietin-1 gene from c.807G>T to 355G>T 2. The duration of male and female contraceptive advice has been changed from at least 13 weeks to at least 24 weeks. This will allow for near-complete elimination of ISIS 721744 as 24 weeks encompasses approximately 5 half-lives of ISIS 721744 and 1 menstrual cycle (requested by the MHRA, to comply with CTFG guidance (Clinical Trial Facilitation Group 2014) 3. To add language that patients who complete Study Visit Week 17, and meet eligibility requirements, may start the Treatment Period in the ISIS 721744-CS3 OLE study anytime after the Week 17 visit and discontinue participation in the CS2 Post-Treatment Evaluation Period at that time 4. To remove as secondary endpoints the time normalized number of HAE attacks (per month) from Week 9 to Week 21 and the time normalized number of moderate or severe HAE attacks (per month) from Week 9 to Week 21, because patients will be allowed to rollover to the ISIS 721744-CS3 OLE study after the Week 17 visit in CS2 5. To remove the requirement that patients must fast before visits that require blood sampling because none of the laboratories listed in Appendix B require fasting and, therefore, fasting is an unnecessary burden for the patient. Minor changes have been made throughout the protocol to correct errors and/or to improve the overall clarity of the original protocol but these changes do not impact subject safety, exposure, or the overall study design.	
Amendment 3	The following modifications to Protocol ISIS 721744-CS2 Amendment 2, dated 29 January 2020, have been made: 1. To adjust the length of time patients must not have received lanadelumab, prior to screening for ISIS 721744-CS2, from 6 months to 10 weeks (i.e., 5 times the ~14-day half life for lanadelumab).	05 May 2020

	2. To decrease the burden of site visits where feasible for patients, Study Drug administration, assessements and procedures may be conducted by either a Home Healthcare professional (if available) or the Study Center, as arranged by the Study Center personnel, for visits as noted in Appendix A. 3. To decrease the burden of PK sampling for patients, only a subgroup of approximately 6 patients (rather than all patients) will have blood draws of pre-dose, 1, 2, 4, and 6 hours post-dose on Day 1 and Day 85. This, along with a pre-dose and a 2 hour post-dose blood collection on Day 1 and Day 85 in all patients, will provide enough information to determine PK parameters. 4. Minor changes have been made throughout the protocol to correct errors and/or to improve the overall clarity of the original protocol but these changes do not impact subject safety, exposure, or the overall study design.	

Statistical Analysis Plan

ISIS 721744-CS2

A Randomized, Double-Blind, Placebo-Controlled, Phase 2a Study to Assess the Clinical Efficacy of ISIS 721744, a Second-Generation Ligand-Conjugated Antisense Inhibitor of Prekallikrein, in Patients with Hereditary Angioedema

Date: Feb 17, 2021

Version: 1.0

Statistical Analysis Plan Signature Page

Ionis Pharmaceuticals, Inc.
2855 Gazelle Court Carlsbad, CA 92010

Compound Name: 721744

Protocol: CS2

Study Title: Randomized, Double-Blind, Placebo-Controlled, Phase 2a Study to Assess the Clinical Efficacy of ISIS 721744, a Second-Generation Ligand-Conjugated Antisense Inhibitor of Prekallikrein, in Patients with Hereditary Angioedema

Issue Date: 5 May 2020 (Protocol Amendment 3)

Signature: _____ Date: _____

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2855 Gazelle Court
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Table of Contents

1 INTRODUCTION

This document provides a description of the study organization, study procedures, and the plan for the statistical analysis of the study data. Section 1 discusses study design, objectives, and endpoints; Section 2 provides the study procedures; Section 3 provides the detailed plan for the statistical analyses.

As with any statistical analysis plan (SAP), the proposed methods and approaches to the data analysis should be viewed as flexible. The statistical analysis to some degree is iterative since so much of the planning is based on statistical and other assumptions, which require verification.

1.1 Study Overview

This is a Phase 2a study, will be conducted at multiple Study Centers worldwide to assess the efficacy of ISIS 721744 in approximately 24 patients with HAE. Part A of the study will be randomized, double-blind, and placebo-controlled; Part B of the study will be open-label. The study will be conducted concurrently in 2 parts (Part A and Part B); patients will be allocated into Part A or Part B according to type of HAE (i.e., either HAE-1/HAE-2 in Part A or HAE-nC1-INH in Part B).

In Part A, approximately 18 patients with HAE-1/HAE-2 will be randomized to SC injections of ISIS 721744 80 mg or placebo in a 2:1 ratio (ISIS 721744:placebo). In Part B, approximately 6 patients with HAE-nC1-INH will be administered open-label SC injections of ISIS 721744 80 mg. Due to the rarity of HAE-nC1-INH, enrollment in Part B may be ended early if study centers are unable to enroll sufficient patients; this will not impact the completion of Part A.

The study will consist of Screening, Treatment, and Post-Treatment Periods. Please refer to the Schedule of Procedures in protocol Appendix A. Patients may be required to attend additional visits for monitoring of AEs or abnormal investigation results. The frequency of additional monitoring will be determined by the Sponsor Medical Monitor in consultation with the Investigator. The length of each patient's participation in the study is approximately 8 months, which includes an up to 8-week Screening Period, a 12-week Treatment Period (patients will receive fixed SC doses of Study Drug every 4 weeks during 4 on-site study visits),and a 4 to 13-week Post-Treatment Period as determined by whether a patient enrolls in the ISIS 721744-CS3 OLE study.

1.2 Objectives

1.2.1 Primary Objective

The primary objective of the study is to evaluate the clinical efficacy of antisense inhibitor of

prekallikrein (ISIS 721744) in patients with hereditary angioedema (HAE) type 1 (HAE-1), HAE type 2 (HAE-2), or HAE with normal C1-inhibitor (HAE-nC1-INH).

1.2.2 Secondary Objectives

The secondary objectives of the study are to evaluate safety and tolerability of ISIS 721744 in patients with HAE-1/HAE-2 or HAE with normal C1-INH (HAE-nC1-INH) and to evaluate the effect of ISIS 721744 on plasma prekallikrein (PKK) and other relevant biomarkers.

1.2.3 Exploratory Objectives

The exploratory objectives of the study are to evaluate pharmacokinetics (PK) of ISIS 721744 (as a total full-length antisense oligonucleotide [ASO], including fully conjugated, partially conjugated, and unconjugated ISIS 721744) over time and to assess potential PK/pharmacodynamic (PD) correlations on relevant biomarkers and clinical outcomes, as appropriate.

1.3 Endpoints

1.3.1 Primary Endpoints

The primary endpoint is the time-normalized number of investigator-confirmed HAE attacks (per month) from Week 1 to Week 17.

1.3.2 Secondary Endpoints

Secondary endpoints include the following:

- The time-normalized number of investigator-confirmed HAE attacks (per month) from Week 5 to Week 17
- The number of patients with a clinical response (defined as a ≥ 50%, ≥ 70%, or ≥ 90% reduction from Baseline in Investigator-confirmed HAE attack rate) by Week 17
- The number of investigator-confirmed HAE attacks requiring acute therapy from Week 5 to Week 17
- Cleaved high molecular weight kininogen (cHK) levels at Weeks 9 and 17
- PKK activity at Weeks 9 and 17
- Consumption of on-demand medication at Weeks 9 and 17
- Angioedema quality of life (AE-QoL) questionnaire score at Weeks 9 and 17

1.3.3 Safety Endpoints

The safety and tolerability of ISIS 721744 will be assessed by determining the number, type,

severity, and dose-relationship of adverse events (AEs); vital signs; electrocardiograms (ECGs); and clinical laboratory parameters. Safety results in patients dosed with ISIS 721744 will be compared to safety results in patients dosed with placebo.

1.3.4 Exploratory Endpoints

- The number of HAE attack-free patients by Week 17
- PK parameters, including, but not limited to maximum observed plasma concentration (C_{max}), time to C_{max} (t_{max}), area under the plasma concentration-time curve (AUC), and half-life ($t_{½}$)
- Potential exposure response analysis using relevant exposure parameters and Biomarkers

1.3.5 Additional Endpoint

- The time-normalized number of moderate or severe investigator-confirmed HAE attacks (per month) from Week 5 to Week 17

2 PROCEDURES

2.1 General Overview of Procedures

Ionis Pharmaceuticals, Inc. will review all study data including source documents, CRFs, and laboratory reports. The study site will enter subject source data into the case report form. Laboratory data will be transferred electronically to Ionis Pharmaceuticals, Inc.

2.2 Randomization & Treatment Allocation

Patients will be allocated into Part A or Part B according to type of HAE (i.e., either HAE-1/HAE-2 in Part A or HAE-nC1-INH in Part B). Only Part A will be randomized and placebo-controlled.

Patients will be enrolled and/or randomized (Part A only) at the Week 1 Visit, after all screening assessments have been completed and after the Investigator has verified that they are eligible per the criteria in protocol Sections 5.1 and 5.2. No patient may begin treatment prior to randomization (Part A only) and assignment of a unique patient identification number.

In Part A, approximately 18 patients with HAE-1/HAE-2 will be randomized via the Interactive Response Technology (IRT) system to SC injections of ISIS 721744 80 mg or placebo in a 2:1 ratio (ISIS 721744:placebo). In Part B, approximately 6 patients with HAE-nC1-INH will be enrolled via the IRT system to receive open-label SC injections of ISIS

721744 80 mg. Due to the rarity of HAE-nC1-INH, enrollment in Part B may be ended early if Study Centers are unable to enroll sufficient patients; this will not impact the completion of Part A.

Randomization information will be concealed from the Investigators and patients until the end of the study, with the exception of an emergency situation involving a patient that requires unblinding of the treatment assignment.

2.3 Conduct

The study will be conducted in accordance with current Good Clinical Practice (GCP) and International Conference on Harmonization (ICH) guidelines, the World Medical Association Declaration of Helsinki guidelines, the Food and Drug Administration (FDA) Code of Federal Regulations, and all other local regulatory requirements.

2.4 Data Monitoring

2.4.1 Safety Data Monitoring

Ionis Pharmaceuticals, Inc. (or designee) is responsible for processing all reported adverse events (AEs). All serious adverse events (SAEs), reported to Ionis Pharmaceuticals, Inc. (or designee), are reviewed according to standard operating procedures. The medical monitor will review all AEs and SAEs on an ongoing basis throughout the study. Ionis Pharmaceuticals, Inc. (or designee) will prepare and submit safety reports to the health authorities worldwide in accordance with local requirements. If it becomes necessary to communicate new safety information, Ionis Pharmaceuticals, Inc. (or designee) will also prepare a safety notification letter and transmit it to study site.

2.4.2 Data Monitoring Board

An independent Data and Safety Monitoring Board (DSMB) will be established to monitor the overall safe conduct of the study. Based on its ongoing assessment of the safety and tolerability of ISIS 721744, the DSMB will provide recommendations to the Sponsor for modifying, stopping or continuing the study as planned. Details on the safety assessments, frequency of review, meeting schedules, and controlled access to unblinded data are outlined in the DSMB Charter.

2.5 Data Management

An electronic case report form (eCRF) utilizing an Electronic Data Capture (EDC) application will be used for this Study.

2.5.1 Case Report Form Data

BioClinica (or designee) is responsible for creating the Electronic Data Capture (EDC) data entry screens, database and edit checks using definitions developed by Ionis Pharmaceuticals, Inc. Ionis Pharmaceuticals, Inc. is responsible for the review, data management querying and locking of the database.

Data are single-entered into the EDC system by the investigator site staff. Programmed edit checks (computer logic that checks the validity of the data entered and also prompts for missing data that is expected to be entered) are run and automatic queries are generated. Ionis Pharmaceuticals, Inc. reviews all data for accuracy and validity and generates additional queries in the EDC system when necessary. The data is corrected or an explanation concerning the query is provided in the EDC system. After all data are entered, reviewed (by Data Management and Clinical Development) and queried, and all queries resolved, the database is locked.

2.5.2 Laboratory Data

Ionis Pharmaceuticals, Inc. is responsible for the format of the laboratory electronic data transfers, transfer schedule and review of the clinical laboratory data. This lab data will be stored as SAS data sets or Excel files.

2.5.3 Pharmacokinetics Data

Ionis Pharmaceuticals, Inc. is responsible for the management and review of the plasma drug concentration data. Final data, which has been approved by Quality Assurance, will be stored in version-controlled repository

3 ANALYTICAL PLAN

3.1 General Overview of Analyses

3.1.1 Statistical Methods

Descriptive summary statistics including number of subjects, mean, median, standard deviation, standard error, interquartile range (25th percentile, 75th percentile), and range (minimum, maximum) for continuous variables, and counts and percentages for categorical variables will be used to summarize most data. All statistical tests will be conducted using 2-sided tests with 5% Type I error rate unless otherwise stated. In view of the exploratory nature of this study, adjustments for multiplicity of testing will generally not be used.

Both central and local lab data will be used in the analyses, including by visit summaries, figures and abnormality summary.

PK parameters will be summarized using number of Subjects, mean, standard deviation, coefficient of variation (CV), geometric mean, geometric %CV, median, minimum, and maximum.

General Presentation Considerations

The minimum and maximum will be reported to the same number of decimal places as the raw data recorded in the database. The mean, median, lower quartile and upper quartile will be reported to one more decimal place than the raw data recorded in the database. The standard deviation will be reported to two more decimal places than the raw data recorded in the database. In general, the maximum number of decimal places reported shall be four for any summary statistic.

Categorical data will be summarized in terms of the number of subjects providing data at the relevant time point (n), frequency counts and percentages. Any planned collapsing ofcategories will be detailed in the text and the data displays.

Percentages will be presented to one decimal place and not be presented for zero counts. Percentages will be calculated using n as the denominator.

P-values greater than or equal to 0.001, in general, will be presented to three decimal places. P-values less than 0.001 will be presented as "<0.001".

Confidence intervals will be presented to one more decimal place than the raw data.

Baseline definition

For platelets, Baseline will be defined as the average of all non-missing pre-dose assessments.

For other assessments, if there are 2 or more pre-dose values available, Baseline will be defined as the average of the pre-dose Study Day 1 value and the last pre-dose value prior to Study Day 1. If there is only 1 pre-dose measurement available, then it will be assigned as Baseline

Run-in Period

The run-in period is defined as the period from screening to first dose of study Drug administration.

On-treatment and Post-treatment Periods

- For HAE attack endpoints:
    - The on-treatment period spans the time during which the study treatment is administered until earliest date from 28 days after the last dose of medication and last contact date within the study.

  - The post-treatment period starts on the day after the on-treatment period and ends on the day of the patient's last contact date within the study.

- For PD (cHK and PKK levels) and AE-QoL:
  - The on-treatment period spans the time during which the study treatment is administered until earliest date from 42 days after the last dose of medication and last contact date within the study.
  - The post-treatment period starts on the day after the on-treatment period and ends on the day of the patient's last contact date within the study.

Analytical visits

PD (cHK, plasma proenzyme activation, and PKK levels) and AE-QoL data will be mapped to analysis visit specified in the table below. The intent of these visit windows is not to align with those prescribed for visit scheduling in the clinical study protocol but, rather, based on the protocol-defined target study day, to delineate mutually exclusive windows so that all assessments proximal to a particular study week can be integrated to best represent the patient's status during that period of the study. Visits after Week 17 are part of the post-treatment assessment period and, due to the fact that most patients are expected to roll into the OLE Study ISIS 721744CS3, these data will only be provided in patient listings for evaluation of individual patient safety rather than being tabulated. Therefore, no visit windows are needed for data analysis for these visits. The PD and AE-QoL assessments that occurred during the post-treatment period (as defined above) will not be included in the PD analyses/summaries, even if they occurred within one of the visit windows. If there are multiple assessments within a visit window, the visit nearest the scheduled date will be used unless 2 visits are equally near, in which case the average will be used.

Assessments	Mapped Visit (Week)	Target Day	Study Day Window
PD	3	15	2-22
	5	29	23-43
	9	57	44-71
	13	85	72-99
	17	113	100-127
AE-QoL	9	57	44-71
	17	113	100-127

Other data will be summarized using the visit labels provided in the data. Multiple results with the same visit label will be averaged. Results with visit labels as "Unscheduled" will not

be included in the by-visit summary tables and figures except for determining baseline and laboratory abnormality summaries but will be presented in data listings.

3.1.2 Subject Population Analyzed

The following analysis populations will be used for the analysis of data as described within each analysis population.

Safety Population

The Safety Population will include all enrolled patients who receive at least 1 dose of Study Drug (ISIS 721744 or placebo).

Intent-to-Treat (ITT) Population

The ITT Population will include all enrolled or randomized patients.

Per Protocol Population

The Per-Protocol (PP) Population will include all patients in the ITT Population who are treated according to the protocol without any major deviations.

PK Population

The PK Population will include all patients who are enrolled and receive at least 1 dose of Study Drug and have at least 1 evaluable PK sample.

In addition to the above analysis populations, it is recognized that some data displays will be provided for "All Screened", "Screening Failures" and "All Randomized" subjects but no data analysis will be executed in these populations except for the disposition table that includes all screened subjects.

3.1.3 Sample Size Consideration

The primary endpoint is the time-normalized number of HAE attacks (per month) from Week 1 to Week 17. From historical data, the placebo group is estimated to have 6.8 HAE attacks per 4-month period. If the ISIS 721744 80 mg group is assumed to have 2.8 HAE attacks per 4-month period, then with a 0.05 significance level and using Poisson model, the sample size of 18 patients (12 patients administered SC injections of ISIS 721744 80 mg and 6 patients administered placebo) will provide at least 90% power for the primary endpoint, considering a 10% missing data or dropout rate for both active treatment and placebo. The sample size of 18 patients with HAE-1/HAE-2 is also considered sufficient for safety and tolerability evaluation.

There is no statistical rationale for the sample size of 6 patients with HAE-nC1-INH.

3.1.4 Planned Interim Analysis

No interim analysis is planned for this study. However, an independent Data Safety Monitoring Board (DSMB) will be established to provide ongoing, independent review and assessment of the safety data, and to safeguard the interests and safety of the participating subjects in the study. Analysis of the data for DSMB review will be conducted according to the DSMB Charter. Because no formal hypothesis testing for safety assessments is planned, multiplicity concerns regarding repeated analyses are not an issue.

3.1.5 Incomplete or Missing Data

All available data will be included in the analysis. The length of observation time will be included as an offset variable in the Poisson model to adjust for differences in follow-up time.

3.1.5.1 Imputing Missing Start or End Date and Time for HAE Attacks

In general, missing start time will be imputed as 0:00 and missing end time will be imputed as 23:59. However, the following rules will be applied for the attacks satisfying the corresponding conditions, in order to conservatively classify the attacks as separate, distinct attacks with at least 24 hours in-between:

- For HAE attacks with a missing start time and a non-missing start date one calendar day after the end date of the previous attack, the start time will be imputed using the end time of the previous HAE attack to ensure there are 24 hours in between the two attacks.
- For HAE attacks with a missing start time and a non-missing end date/time within 24 hours from the end date/time of the previous attack, the attack should be considered as one attack with the previous attack
- For HAE attacks with missing end time and a non-missing end date one calendar day before the start date of the next attack, the end time will be imputed as the start time of the next HAE attack to ensure there are 24 hours in between the two attacks.
- For HAE attacks with a missing end time and non-missing start date/time within 24 hours from the start date/time of the next attack, the attack should be considered as one attack with the next attack.

For HAE attacks with a non-missing start date and time and a missing stop date and time:

- The stop date and time will be imputed as the earlier of the following two date and time:
    - Start date and time + 48 hours or study completion date and the stop time of 23:59, whichever is later.
    - 24 hours before the start date and time of the next attack.

3.1.6 Unique HAE Attacks

To be counted as a unique attack distinct from the previous attack, the new symptoms must occur at least 24 hours after resolution of the prior attack's symptoms.

Specifically, there must be at least 24 hours between the stop date/ time of the first event and the start date/time of the next event, for the attacks to be considered distinct. If there is less than 24 hours between the stop date/time of the first event and the start date/time of the next event, the events will be counted as one attack.

When two or more attacks are combined for efficacy analysis, the parameters of the attacks will be conservatively chosen. The start date and time of the combined attack will take the earliest start date and time from the individual attacks; and the end date and time of the combined attack will take the latest end date and time of the individual attacks. The severity of the combined attack will take the highest severity from the individual attacks. The primary location of the combined attack will be determined by the primary location of the individual attacks, and by following the hierarchy of laryngeal attack, peripheral attack, and abdominal attack. One primary location will be taken; and all the other primary location(s) and secondary locations will be considered as secondary location for the combined attack. The rescue medications and supportive treatment for the combined attack will include all the records from individual attacks. Also, the combined attack will be considered as an investigator-confirmed attack if any of the individual attack being combined is an investigator-confirmed attack.

3.2 Demographic and Baseline Characteristics and Patient Disposition

Baseline and demographic variables will be summarized descriptively by treatment group and overall for Part A, overall for Part B, and for each analysis population.

Demographic and baseline characteristics to be presented include age, age category (18-<40, 40 to 64, ≥65 years), gender, race, ethnicity, height, weight, BMI, type of genetic mutation.

Age will be calculated as the difference between informed consent date and patient birth date divided by 365.25 and rounded down to the associated integer value.

For race summary, if multiple races are recorded in database, 'Multiple Race' will be used in the summary table but details records in the listing.

A separate table will be created for HAE history and will include family history of HAE, age at onset of angioedema symptoms, HAE type, type of attack(s) experienced, Lanadelumab use,

reason for discontinuation of Lanadelumab, number of attacks in the last 12 months, run-in period HAE attack rate (attacks/4 weeks), run-in period HAE attack rate group (1 to <2, 2 to <3, ≥3 attacks/4weeks).

The run-in period HAE attack rate will be calculated for each subject as number of HAE attacks occurring during the run-in period divided by the number of days the subject contributed to the run-in period multiplied by 28 days.

Medical history will be provided in the data listings.

Subject enrollment and disposition will be summarized by treatment group and overall for Part A, and overall for Part B.

The summaries will include: the total number of screened subjects, the number of randomized (Part A) or enrolled (Part B) subjects, the number of subjects in each analysis population (with the exception of the PK Set), the number of subjects completing treatment, the primary reason for terminating treatment, the number of subjects completing post-treatment follow-up, and the primary reason for terminating post-treatment follow-up.

3.3 Efficacy Analyses

All efficacy analyses will be performed on the ITT population and Per-protocol population, with the former being the basis for the primary efficacy analysis.

3.3.1 Analysis of Primary Endpoint

The primary efficacy endpoint is the time-normalized number of investigator-confirmed HAE attacks per month (defined as 28 days) during the on-treatment period from Week 1 to Week 17 (28 days after last dose administration), will be compared between ISIS 721744 80 mg and placebo in Part A using a Poisson regression model and Pearson chi-square scaling of standard errors to account for potential overdispersion. The model will include fixed effect for treatment group (categorical), the time normalized run-in period attack rate (continuous) as a covariate, and the logarithm of time in month (days from first dose date to 28 days after last dose administration divided by 28) that each subject was observed during the period will be used as an offset variable.

The primary analysis of the primary endpoint will be conducted in the ITT population.

See Section 3.2 for the calculation of the normalized run-in period attack rate.

From this model, the least squares mean rate and standard error for each treatment group as well as, the mean rate ratios relative to the placebo group and corresponding 95% confidence intervals will be estimated. The p-value of Wald-based chi-square test will also be reported. The percentage difference in mean investigator-confirmed HAE attack rate between ISIS 721744 80 mg and placebo will be calculated as 100% * (mean rate ratio –1). Similarly, the estimated upper and lower confidence limits for the mean rate ratio can be transformed by subtracting 1 and multiplying by 100% to calculate 95% confidence intervals for the percentage change.

Below is the SAS code for the primary analysis:

```
PROC GENMOD;
  CLASS arm;
  MODEL no_attks = arm baserate / DIST=poisson LINK=log OFFSET=logmon PSCALE;
  LSMEANS arm/ DIFF CL EXP ILINK;
RUN;
```

Where:
arm= treatment arm (categorical)
no_attks = number of HAE attacks during the analysis period
baserate = normalized HAE attack rate during the run-in period (continuous)
logmon = logarithm of time in month each patient was observed during the analysis period.

If one treatment group has 0 count, Fisher's Exact Test will be used for the analysis instead of Poisson regression. The odds ratio, corresponding 95% CI, and p-value will be provided.

The following sensitivity analyses will be performed on the primary efficacy endpoint to evaluate the robustness of the results.

1. The primary analysis described above will be repeated in the PPS as a sensitivity analysis.

2. The primary efficacy endpoint will be compared between ISIS 721744 80 mg and placebo in Part A using a Negative Binomial model. The model will include fixed effects for treatment group (categorical), the time normalized run-in period attack rate (continuous) as a covariate, and the logarithm of time in month (days from first dose date to 28 days after last dose administration divided by 28) that each patient was observed during the on-treatment period will be used as an offset variable. The analysis will be conducted in the ITT population.

   Below is the SAS code for the sensitivity analysis:

```
PROC GENMOD;
  CLASS arm;
  MODEL no_attks = arm baserate / DIST= NEGBIN OFFSET=logmon;
  LSMEANS arm/ DIFF CL EXP ILINK;
RUN;
```

Where:
arm= treatment arm (categorical)
no_attks = number of HAE attacks during the analysis period
baserate = normalized HAE attack rate during the run-in period (continuous)
logmon = logarithm of time in month each patient was observed during the analysis period

The Part B data will be summarized using descriptive statistics. The exact 95% CI for mean based on the gamma distribution will be reported.

In addition to the model-based analysis described above, unadjusted monthly investigator-confirmed HAE attack rates from Week 1 to Week 17 (end of the on-treatment period) as well as change and percent change from baseline will be summarized by treatment group and by Part. The monthly investigator-confirmed HAE attack rate will be calculated for each patient as the number of HAE attacks occurring during from Week 1 to Week 17 (end of the on-treatment period) divided by number of days the patient contributed to the period multiplied by 28 days. The mean percent change from baseline on HAE attacks by study month and treatment group will be plotted.

The number of investigator-confirmed HAE attacks per month from Week 1 to Week 17 (end of the on-treatment period) will be also summarized descriptively by month (per 28-day interval) and treatment group and by Part. The summary will include the monthly investigator-confirmed HAE attack rate, change from run-in period, and percent change from run-in period of investigator-confirmed HAE attack rate. Investigator-confirmed HAE attacks will be grouped into 28-day intervals using the start date of the HAE attack. The date of the first exposure to study drug will be used as the start of the first interval and end of the interval will be the date of first exposure to study drug plus 28 days. Each successive interval will start the last day of the prior interval plus 1 day and end 28 days later.

3.3.2 Analysis of Secondary Endpoints

3.3.2.1 Time-normalized number of investigator-confirmed HAE attacks (per month) from Week 5 to Week 17

It will be analyzed using the same method as described for the primary efficacy endpoint, will be conducted in both ITT and Per-protocol populations. Data summaries will parallel those described for the primary analysis of the primary efficacy endpoint. Only patients who

complete Week 5 (29 days) HAE assessments will be included in the analysis. The logarithm of time in month from Week 5 (Day 29) to Week 17 (end of the on-treatment period) for each patient will be used as an offset variable in the model.

3.3.2.2 Time-normalized number of moderate or severe investigator-confirmed HAE attacks (per month) from Week 5 to Week 17

It will be analyzed using the same method as described for the primary efficacy endpoint, will be conducted in both ITT and Per-protocol populations. Only patients who complete Week 5 (29 days) of HAE assessments will be included in the analysis. The logarithm of time in month from Week 5 (Day 29) to Week 17 (end of the on-treatment period) for each patient will be used as an offset variable in the model.

3.3.2.3 The number of patients with a clinical response (defined as a ≥ 50%, ≥ 70%, or ≥ 90% reduction from Baseline in HAE attack rate) by Week 17

For each patient, a treatment period HAE attack rate from Week 5 to Week 17 and run-in period HAE attack rate will be calculated. The percentage reduction will be calculated as the treatment period HAE attack rate from Week 5 to Week 17minus the run-in period HAE attackrate divided by the run-in period HAE attack rate. Patients who discontinued treatment early due to lack of efficacy or AEs will be considered as non-responders and included in the denominator for the calculation of the proportion in the ITT population. Patients who discontinued due to other reason will be excluded from analysis.

Risk difference comparing ISIS 721744 80 mg group to the placebo group in Part A, and corresponding exact 95% confidence interval (Santner and Snell 1980) will be provided. The Fisher's Exact test p-value will also be reported. The analysis will be conducted in both ITT and Per-protocol populations.

Below is the SAS code for this analysis:

```
PROC FREQ;
  TABLES arm*attack / RISKDIFF;
  EXACT RISKDIFF;
RUN;
```

3.3.2.4 The number of investigator-confirmed HAE attacks requiring acute therapy from Week 5 to Week 17

It will be analyzed using the same method as described for the primary efficacy endpoint, will be conducted in both ITT and Per-protocol populations. HAE attacks requiring acute therapy include those attacks with medical intervention or hospitalization marked on the CRFs.

3.3.2.5 Change and Percent Change in cHK and PKK levels at Week 5 to Week 17

The change and percent change from baseline in cHK and PKK levels at each visit during the treatment period will be compared between ISIS 721744 80 mg and placebo in Part A using the Mixed Effects Model with Repeated Measures (MMRM) model. The response variable is the change or percent change from baseline at post-baseline visit up to Week 17. For patients who terminate treatment early, only the data collected up to 42 days after last dose administration will be included. The MMRM model will include effects of treatment (ISIS 721744 or placebo), time (categorical), treatment-by-time interaction, and baseline value. The analysis will be conducted in both ITT and Per-protocol populations. The unstructured covariance model will be used to model the within patient errors, shared across treatments and small sample adjustments to standard errors and tests will be made following the Kenward-Roger approach (Kenward, M. G. and Roger, J. H. (1997). If there are convergence problems with the repeated measures mixed model, this will be explored. For example, the SCORING=4 option could be used in the PROC MIXED statement in SAS. This makes SAS use Fisher scoring for the first 4 iterations. If the convergence problem cannot be resolved the unstructured covariance matrix will be replaced by the compound symmetry covariance matrix (Type=CS in SAS).

Below is the SAS code for this analysis:

```
PROC MIXED;
  CLASS arm visit subject;
  MODEL endpoint=arm baseline visit arm*visit/ DDFM=kr;
  REPEATED visit / SUBJECT=subject TYPE=un;
  LSMEANS arm*visit / CL DIFF;
RUN;
```

The normality of each parameter will be examined using the Shapiro–Wilk test. The non-parametric Wilcoxon Rank Sum test will also be performed at each visit as the sensitivity analysis. Hodges-Lehmann estimates of the differences between ISIS 721744 80 mg group and the placebo group in Part A as well as distribution-free CIs based on the Wilcoxon Rank Sum Test will also be provided.

CHK and PKK levels as well as the change and percent changes from baseline over time will also be summarized using descriptive statistics by visit, treatment group and by Part.

The change and percent change in plasma proenzyme activation levels will also be analyzed.

3.3.2.6 Consumption of on-demand medication by Weeks 9 and 17

The number and percentage of patients who used on-demand medication by Week 9 (Day 57) and by Week 17 (end of the on-treatment period) will be tabulated by treatment group and by Part. On-demand medications will be identified based on manual review.

3.3.2.7 AE-QoL score at Weeks 9 and 17

AE-QoL will be evaluated by determining its four individual domain scores and a total score. Each item answered by the patient scores between 0 and 4 points depending on the answer option chosen by the patient. The first answer option gets 0 points, the second option 1 point, the third option 2 points, etc. The AE-QoL domain scores and total score are calculated by using the following formula:

(Sum of all completed items) / (maximum sum of all possible items)*100

Computation of AE-QoL Total Score
Example 1: All items were completed (maximum possible sum: 68 points)
Sum of all 17 completed items: 41 points.
Total score = 100*(41/68) = 60 (out of a possible 100 points)

Example 2: 2 items were not completed (maximum possible sum: 60 points).
Sum of all 15 completed items: 41 points.
Total score = 100*(41/60) = 68 (out of a possible 100 points)

Computation of Domain Scores (Example: Fears/Shame)
Example: Sum of all 6 completed items: 14 points
Maximum possible sum: 24 points
Domain Score = 100*(14/24) = 58 (out of a possible 100 points)
Remarks
Since only answered items are included in the computation (and the calculated domain and total scores are not raw scores but linear transformations to a 0-to-100 scale), the calculated scores are not or only little influenced by missing items.

An AE-QoL domain score should not be calculated if more than one item is left unanswered in that domain. The AE-QoL total score should not be calculated if more than 25% of items (>4 items) are left unanswered.
The minimal and highest possible domain and total scores are 0 and 100, respectively.

The AE-QoL total score and domain score will be analyzed using the same method as described for cHK, will be conducted in both ITT and Per-protocol population.

3.3.3 Analysis of Exploratory Endpoints

3.3.3.1 The number of HAE attack-free patient by Week 17

The number and percentage of patients who achieve investigator-confirmed HAE attack free (no investigator confirmed HAE attacks) by Week 17 (end of the on-treatment period) will be tabulated by treatment group and by Part. Patients who discontinued treatment early due to lack of efficacy or AEs will be considered as non-responders and included in the denominator for the calculation of the proportion in the ITT population. Patients who discontinued due to other reason will be excluded from analysis. The risk difference between ISIS 721744 80 mg group to the placebo group in Part A, and the corresponding exact 95% confidence interval will be provided. The Fisher's Exact test p-value will also be reported. The analysis will be conducted in both ITT and Per-protocol population.

The number and percentage of patients who achieve investigator-confirmed HAE attack free (no investigator confirmed HAE attacks) between Week 5 to the end of the on-treatment period, between Week 9 to the end of the on-treatment period, and between Week 13 to the end of the on-treatment period will also be tabulated and analyzed in a similar manner.

3.3.4 Analysis of Additional Endpoint

3.3.4.1 Time-normalized number of moderate or severe investigator-confirmed HAE attacks (per month) from Week 1 to Week 17

It will be analyzed using the same method as described for the primary efficacy endpoint, will be conducted in both ITT and Per-protocol populations.

3.4 Safety Analyses

Safety analyses will be performed on the safety population.

3.4.1 Exposure

Treatment duration, number of doses and amount of Study Drug will be summarized by Part and treatment group.

The treatment duration (days) for each patient is defined as last dose date - first dose date +1.

3.4.2 Adverse Events

An adverse event will be regarded as treatment emergent if it is present prior to receiving the first dose of study drug and subsequently worsens, or is not present prior to receiving the first dose of study drug but subsequently appears.

To determine the AE as treatment-emergent or not, if there is no "Formlink" link, and the AE (start date/time) occurs on or after the patient's first dosing date/time, then the AE is treatment-emergent. Otherwise, if the AE (start date/time) occurs prior to the patient's first dosing date/time, then the AE is not treatment-emergent.

If there is a "Formlink" link between two AE records, then we compare them pairwise, and consider two cases, where we compare the AE severity (mild/moderate/severe) between the two records in the pair. We chronologically order the 2 records (by AE start date) and refer to the "first" and "second" AE.

Case 1: The first AE record in the pair occurs before first dosing, and the second AE record occurs after first dosing.

If the AE severity of the second record is worse than that of the first record, then only the second AE is deemed as a TEAE. Otherwise, neither record is considered as TEAE.

Case 2: Both AE records in the pair occur after first dosing.

If the AE severity on the second record is worse than the severity on the first record, then count both records as treatment-emergent. But, if the severity improves, then only count the first record as treatment-emergent.

When counting the total number of treatment-emergent events, events linked together through change in severity will still be counted as separate events.

All TEAEs identified based on the rules above will be summarized in the event number analysis.

The most conservative approach will be used to determine if the event occurs after the treatment. For example, if the onset date or resolution date of an AE is prior to the first study treatment date, it will be considered to have occurred prior to the study period. If the onset or resolution date of an AE is a partial date with only month or year available or complete missing, then the event is assumed to be within the study period unless the year is prior to the year of the first study treatment date, or if in the same year, the month is prior to the month of the first study treatment date.

The incidence of AEs will be summarized by Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class for:

- Any treatment emergent adverse events
- Related treatment emergent adverse events. Related is defined as "Related", "Possible", or missing relationship to study drug
- Any treatment emergent adverse events by severity. At each level of patient summarization, a patient is classified according to the highest severity if the patient reported one or more events. Adverse events with missing severity will categorized as "Missing" for this summary
- Related treatment emergent adverse events by severity
- Serious treatment emergent adverse events
- Serious and related treatment emergent adverse events

AEs that lead to study discontinuation or investigational drug discontinuation will be listed. Non-treatment emergent adverse event will be flagged in the data listing.

Local Cutaneous Reactions at the Injection Site

Local cutaneous reaction at injection site (LCRIS) is defined as (A) moderate or severe adverse events with the preferred terms (PTs) Injection site erythema, Injection site swelling, Injection site pruritus, or Injection site pain that started on the day of injection, persisted for at least two days or ongoing; or (B) any AE at the Study Drug injection site, regardless of severity, that leads to discontinuation of study drug, where AE at the Study Drug injection site is the principal reason for discontinuation. LCRIS will be summarized using the MedDRA coding system, by PT and by treatment group and Part. Patients with moderate, severe and any LCRIS will also be summarized. Discontinuations due to AE at the injection site will be summarized separately.

Percentage of injections leading to those events will be summarized by PT and overall using the descriptive statistics. Additionally, percentage of injections leading to events will be summarized by moderate, severe severity and overall discontinuation of study drug due to AE at injection site.

Percentage of injections leading to LCRIS at the injection site will be calculated as follows for each patient: (A/B)*100, where A=number of injections with a LCRIS, and B=total number of injections. Doses that are split across multiple injections are counted as a single injection.

LCRIS will also be listed.

Flu-like Reactions

Flu-like reactions are defined as adverse events with PTs including either (A) Influenza like illness or (B) Pyrexia or Feeling hot or Body temperature increased, plus at least two of the following symptoms with the PTs: Chills, Myalgia, or Arthralgia, starting on day of injection or the next day.

Flu-like reactions will also be summarized using the MedDRA coding system, by preferred term and by treatment group and part.

Percentage of injections leading to flu-like reactions will be summarized by treatment group and by Part using the descriptive statistics.

Percentage of the injections leading to flu-like reactions will be calculated as follows for each patient: (A/B)*100, where A=number of injections leading to flu-like reactions, and B=total number of injections.

Flu-like reactions will also be listed.

Bleeding Adverse Events

Bleeding AEs will be identified based on the Haemorrhages (SMQ) Export from MedDRA and summarized by MedDRA system organ class and preferred term and by treatment group and part.

3.4.3 Laboratory Measurements

The following is the list of lab analytes that will be collected throughout the study:

- Chemistry: sodium, potassium, chloride, bicarbonate, total protein, albumin, calcium, magnesium, phosphorus, glucose, BUN, creatinine, cholesterol, uric acid, total bilirubin, direct (conjugated) bilirubin, indirect (unconjugated) bilirubin, ALT, AST, alkaline phosphatase, creatine kinase, GGT,
- Hematology: red blood cells, hemoglobin, hematocrit, platelets, MCV, MCH, MCHC, platelets, white blood cells (WBC), and WBC differential (percentage and absolute count) (basophils, eosinophils, lymphocytes, monocytes and neutrophils)
- Coagulation: aPTT (sec): PT (sec), INR, Plasmin-antiplasmin complexes, D-dimer
- Complement: Bb, C5a, C4 split products, C4
- Inflammatory: Hs-CRP
- Screening tests: hepatitis B surface antigen, hepatitis C antibody, HIV antibody, FSH (women only, if applicable), and serum βhCG (women only) The data will only be displayed in subject listings.

- Urinalysis (other): color, appearance, specific gravity, pH, P/C ratio, protein, blood, ketones, urobilinogen, glucose, bilirubin, , leukocyte esterase, nitrate, eGFR, microscopic examination. The data will only be displayed in subject listings.

Missing WBC differential absolute counts and percentages will be derived:
If WBC differential absolute counts are missing, and percentages are available, then absolute counts will be calculated by multiplying the percentage by total WBC count. Conversely, if absolute count is available, and percentage is missing, then percentage will be calculated by dividing absolute count by the total WBC count. If WBC differential absolute counts are missing, and manual count values are available, then manual count values will be used. If neutrophils count and percentages are missing, and segmented neutrophil and band neutrophil results are available, then neutrophils will be calculated by adding segmented neutrophils and band neutrophils, if only segmented neutrophil result is available, then neutrophils will be set to segmented neutrophils result.

All lab data will be displayed in subject listings.

Chemistry, hematology, coagulation, and complement, (result, change and percent change from baseline) will be summarized using descriptive statistics (n, mean, median, standard error, standard deviation, Q1, Q3, minimum, and maximum) by treatment group and study visit.

For ALT and AST, the number and percent of subjects falling in each of the following categories based on the confirmed results will be tabulated by treatment group

- ALT/AST > 3 x ULN, which is confirmed
- ALT/AST > 5 x ULN, which is confirmed

For platelet, the number and percentage of patients falling in each of the following categories based on the confirmed results will be tabulated by treatment group for 100,000/mm^3 to <140,000/mm^3, 75,000 to <100,000/mm^3, 50,000 to <75,000/mm^3, 25,000 to <50,000/mm^3, 0 to <25,000/mm^3.

A confirmed value is based on a consecutive lab value within 7 days. If that value is in the same or worse category the initial value is confirmed. If the consecutive value is in a better category, then the initial value is confirmed using the consecutive value category. If there is no retest within 7 days, then the initial value is presumed confirmed. If there are multiple results on the same day, no matter from the same lab vendor or different lab vendors, then the worst value will be utilized in the analysis.

3.4.4 Vital Signs, Weight, and BMI

Vital signs will include heart rate, respiratory rate, body temperature, systolic and diastolic blood pressure and pulse pressure. Summary tables will be created to present the descriptive statistics (n, mean, standard error, standard deviation, median, Q1, Q3, minimum, and maximum) for vital sign values, weight, and BMI as well as the change and percent change from baseline at each study visits.

3.4.5 Physical Examinations

Adverse changes in physical examinations that are deemed clinically significant by the Investigator will be classified as adverse events. All physical examination data will be provided in a data listing.

3.4.6 12-Lead Electrocardiograms (ECG)

Safety 12-lead ECG will be performed at the visits Screening, Day 1 (Pre-Dose), Day 57, Day 113 and Day 176. The ECG data will include Ventricular Rate, PR Interval, QRS Duration, QTc, QTcF (QT corrected using the Fridericia's formula), QTcB (QT corrected using the Bazett's formula), and Overall interpretation. QTcF and QTcB will be calculated based on the patient's reportable ECG data at each time point using the formula described below:

$QTcF = QT / (RR)^{1/3}$, where RR= 60/VR

$QTcB = QT / (RR)^{1/2}$, where RR= 60/VR

For the continuous variables above, descriptive statistics (n, mean, standard error, standard deviation, median, 25th percentile, 75th percentile, minimum and maximum) of the results at each study visit, as well as the changes and percent changes from Baseline to each study visit, will be presented in summary tables; for the categorical responses to overall interpretation, the results and the associated findings at each visit will be summarized by counts and percentages.

All the safety ECG data collected will be listed.

3.4.7 Prior and Concomitant Medications

Prior medications include medications started prior to the first dose of study medication regardless whether continued while on treatment or not. Concomitant medications include medications that patients are exposed to on or after the first dose of study medication. Partial or missing medication start date or end date will be imputed by the following imputation rules:

Start date:

- If year, month and day are all missing then assign the date of first dose of Study Drug
- If month and day are missing and year is:

- earlier than the year of the first dose of Study Drug then assign December 31
- otherwise, assign January 1

- If only day is missing and month-year is:
  - earlier than the month-year of the first dose of Study Drug then assign the last day of the month
  - otherwise, assign the first day of the month

End date: imputation will be performed for the end date only if the day or month is missing (i.e., year is present):

- If month and day are missing, then assign December 31
- If only day is missing, then assign the last day of the month

If the imputed start date is later than the imputed end date, then set the imputed start date to the imputed end date.

Prior and concomitant medications will be coded using WHO Drug dictionary and summarized by ATC class, preferred name and by treatment group and Part.

3.4.8 Angioedema Activity Score

The AAS consists of 5 questions as well as an opening question. A score between 0 and 3 is assigned to every answer field. The question scores are summed up to an AAS day sum score, 7 AAS day sum scores to an AAS week sum score (AAS7), and 4 ASS week sum scores may be summed up to an AAS 4-week sum score (AAS28). Accordingly, the minimum and maximum possible AAS scores are 0-15 (AAS day sum score), 0-105 (AAS7), and 0-420 (AAS28). Missing scores will be imputed using the LOCF method.

The opening question may be used to count the number of angioedema affected days during the AAS documentation period but has no score.

The AAS scores will be listed. The AAS 4-week sum score will also be summarized by treatment group and by Part over time. In addition, the AAS 4-week sum score will be analyzed using an ANCOVA model, including treatment group as effect, and baseline AAS score as covariate.

3.5 Pharmacokinetic Analysis

The plasma pharmacokinetics of ISIS 721744 (as total full-length oligonucleotides or ISIS 721744-equivalent, ISIS 721744-eq.) will be assessed following SC administration(s).

3.5.1 Plasma Concentration Data of Total Full Length Oligonucleotides

Plasma concentrations of ISIS 721744 (ISIS 721744 eq.), along with the scheduled (nominal) and actual samples times (i.e., time from SC dosing) will be listed (when applicable) for each patient, by treatment group, nominal dose, and day. In addition, percent differences between scheduled and actual sampling times will also be listed for all patients. Percent differences between actual administered dose and nominal dose will also be listed.

Plasma concentrations below the lower limit of quantification (LLOQ) will be indicated by "BLQ". For the purpose of calculating typical descriptive statistics (n, mean, SD, %CV, geometric mean, geometric %CV, median, minimum, and maximum) for plasma concentrations, all BLQ values will be set to zero. Mean plasma concentrations that are BLQ will be presented as "BLQ", and the SD and %CV will be reported as not applicable. Summary statistics of the ISIS 721744 plasma concentrations will be tabulated by treatment group, nominal dose, day, and scheduled time point. At the discretion of the pharmacokineticist and/or biostatistician, samples may be excluded from descriptive statistics if there are large deviations between scheduled and actual sampling times, or large deviations between actual dose and nominal dose.

ISIS 721744 eq. plasma concentration versus time (actual) profiles for each patient that received ISIS 721744 active treatment, as well as the mean (± SD or SE) plasma concentrations versus time (scheduled) profiles, will be presented graphically on linear and semilogarithmic scales. At the discretion of the pharmacokineticist and/or biostatistician, samples may be excluded from the mean plots if there are large deviations between scheduled and actual sampling times.

3.5.2 Plasma Pharmacokinetic Parameters

The plasma PK of ISIS 721744 (as total full-length oligonucleotides) will be assessed following SC administration. Non-compartmental PK analysis of ISIS 721744 (total full-length oligonucleotides) will be carried out on each individual subject data set using Phoenix WinNonlin version 8.0 or higher (Pharsight Corporation, Mountain View, CA). For calculation of PK parameters, all BLQ values will be set to zero. The plasma PK parameters for ISIS 721744-eq. will be calculated based on actual sampling times. The plasma PK parameters to be calculated or determined (when applicable) are listed in Table 1. Other plasma PK parameters, as appropriate, may be determined or calculated at the discretion of the PK scientist.

Table 1 Plasma Pharmacokinetic Parameters to be Calculated or Determined

Parameter	Definition/Method	Day 1	D85
C_{max}	Maximum observed concentration	X	X
T_{max}	Observed time at which C_{max} occurs	X	X
T_{last}	Time of last measurable (positive) concentration	X	X
AUC_{last}	Area under the concentration-time curve from time zero to T_{last}, calculated using linear-up log-down method.	X	
AUC_{0-t}	Partial AUC: Area under the concentration-time curve from time zero to time t (e.g., t may be 24, 48, 72, 168 hrs or 28 days, as applicable), calculated using linear-up log-down method	X	X
AUC_{τ}	Area under the concentration-time curve within the dosing interval (τ) at steady-state, calculated using linear-up log-down method		X
$t_{1/2\lambda z}$	Terminal elimination half-life determined from the equation: ln 2/λ_z, where λ_z is the first-order rate constant associated with the terminal (log-linear) elimination phase. This is estimated via linear regression of time vs. log concentration. A minimum of three data points in the elimination phase will be used to define λ_z and the correlation of determination values (r^2) had to be at or greater than 0.8 for the estimate to be accepted.		X
CL_{ss}/F	Steady-state clearance divided by F (fraction of the dose absorbed) determined by Dose/AUC_{τ}		X
CL_{0-t}/F	Clearance after first dose divided by F (fraction of the dose absorbed) determined by Dose/AUC_{0-t}	X	
V_z/F	Volume of distribution (based on the terminal phase) divided by F (fraction of the dose absorbed)		X

Note: X designates parameters to be calculated or determined assuming sufficient data

Plasma pharmacokinetic parameters will be summarized using descriptive statistics (n, mean, SD, %CV, geometric mean, geometric %CV, median, minimum, and maximum) by treatment group, nominal dose, and day. Additionally, the relationship between dose and plasma exposure parameters (C_{max} and AUC) of total full-length ASOs (ISIS 721744-eq.) will be evaluated using linear-regression analysis of the log-transformed mean data. Lastly, the relationship between individual subject trough data at selected time points and plasma exposure parameters (C_{max} and AUC) will also be evaluated.

3.5.3 Pharmacokinetic/Pharmacodynamic Exposure-Response Analysis

Exposure-response correlations may be explored graphically between plasma exposure (AUC, Cmax, Ctrough, as appropriate), and selected PD measures and outcomes, as well as other relevant biomarkers (such as plasma prekallikrein (PKK), etc.). In addition, the relationship between relevant PD markers and outcomes and plasma trough concentrations of ISIS 721744 will be further evaluated with an inhibitory effect E_{max} model or another exposure-response model as appropriate.

Population PK and PKPD analysis may be performed using the PK and PD data from this Study, and/or combined with other ISIS 721744 clinical PK data later in the development timeline.

3.4.5 Immunogenicity (IM) Analysis

Immunogenicity (IM) analyses will be conducted in the Safety Population. Samples collected pre-dose on Days 1, 29 and 57 and anytime on Days 15, 113, and 176, including early termination samples for IM assessment, may be analyzed for anti-ISIS 721744 antibodies (ADA). In addition, plasma samples collected at other time points (for PK purposes) may also potentially be evaluated if deemed of further interest and warranted by the pharmacokinetic scientist. An evaluable sample will be designated 'IM positive' based on both positive screening and confirmation assay results (i.e., confirmed positive result), and otherwise will be deemed 'IM negative'. Sample IM results (screen positive/negative, confirmed positive/negative or unevaluable, and when applicable, titer of anti-ISIS 721744 antibodies) before, during, and after treatment with study drug (ISIS 721744 or placebo) (sample IM status) will be listed by treatment and dose. The sample ADA incidence (number) and incidence rate (percent) at each evaluated study time point will be determined and appropriately summarized by treatment and dose as the total number of and percentage of evaluated subjects with sample ADA negative, positive, and unknown status. Furthermore, titer over time will be also appropriately summarized (using descriptive statistics) as median, quartiles (25% and 75%), and range by treatment and dose.

Study subjects' overall ADA status will be assigned 'IM positive' status if they have at least one confirmed positive sample result at any time during the treatment or post-treatment evaluation periods. Study subjects will be assigned 'IM negative' status if all evaluated IM sample results during the treatment and post-treatment evaluation periods are IM negative and they have at least one evaluable IM result collected post study drug treatment. Otherwise, a study subject will be assigned 'unknown' IM status. Furthermore, subjects with positive overall ADA status will be further classified into different ADA types based on their baseline ADA status and change in ADA titer post treatment as described below (Shankar et al., 2014):

- Treatment-Emergent ADA: sum of treatment-induced ADA and treatment-boosted ADA as described below:
    - Treatment-Induced ADA: ADA developed de novo (seroconversion) following biologic drug administration (i.e., formation of ADA any time after the initial drug administration in a subject without pre-existing ADA, i.e., baseline negative ADA)
    - Treatment-Boosted ADA: pre-existing ADA that were boosted to a higher level following biologic drug administration (i.e., any time after the initial drug administration the ADA titer is greater than the baseline titer by a factor of 8-fold or more

- Treatment-Unaffected ADA: pre-existing ADA that were not affected (boosted) following biologic drug administration (i.e., any time after the initial drug administration the ADA titer is 4-fold or less)
- ADA type would be not applicable (NA) if the subject overall ADA status is negative.
-

Other subject level IM parameters to be calculated/defined may include but not limited to:

- Subject ADA Status at Baseline: "Positive" if the subject has Week 1 Day 1 pre-dose sample (baseline) tested as confirmed positive; "Negative" if the subject has Week 1 Day 1 pre-dose sample (baseline) tested as confirmed negative; "Unknown" if the subject has Week 1 Day 1 pre-dose sample (baseline) unevaluable.
- Onset of ADA: i.e., the first day ADA positive sample observed, will be calculated by: the date of first sample has “positive” sample IM status - first dose date +1
- Last Positive ADA Study Day: the last positive ADA sample observed from the start of study drug treatment and will be calculated by: the date of last sample has “positive” sample IM status - first dose date +1
- Last IM Sampling Study Day :the last ADA sample collected from the start of study drug treatment and will be calculated by: the date of last sample collected - first dose date +1
- Peak titer: the highest titer observed for the subject
- Time to peak titer: the time to reach peak titer will be calculated by: the date of first peak titer observed- first dose date +1
- Total number of ADA Positive Samples: the total number of ADA samples being confirmed positive for the subject
- Total number of ADA Samples evaluated: the total number of ADA samples being collected and analyzed successfully with reportable results for the subject

Other immunogenicity data analysis may be conducted (e.g. classification as transient or persistent status for IM positive subjects) if there are a sufficient number of subjects with transient IM status. Transient and Persistent ADA definitions are defined below:
Transient ADA response will be defined as:

- Treatment-induced ADA detected only at one sampling time point during the treatment or follow-up observation period (excluding the last sampling time point, which will be considered persistent unless shown to be undetectable at a later time) or
- Treatment-induced ADA detected at two or more sampling time points during the treatment (including follow-up period if any), where the first and last ADA-positive samples (irrespective of any negative samples in between) are separated by a period less than 16 weeks, and the subject’s last sampling time point is ADA-negative.

Persistent ADA response will be defined as:

- Treatment-induced ADA detected at two or more sampling time points during the treatment (including follow-up period if any), where the first and last ADA-positive samples (irrespective of any negative samples in between) are separated by a period of 16 weeks or longer or
- Treatment-induced ADA detected only at the last sampling time point of the study treatment period or at a sampling time point with less than 16 weeks before an ADA-negative last sample.

The subject level ADA prevalence, incidence, and positive ADA response being transient or persistent (if applicable) will be calculated as the number and the proportion (percent) of the study population during the study period by treatment and dose. Subject level IM parameters (as described above) will be listed by treatment and dose for all evaluable subjects, and also appropriately summarized (using descriptive statistics) as median, quartiles (25% and 75%) and range, by treatment and dose.

In addition to PK assessments (Section 3.5.2), selected safety (Section 3.4) and PD assessments (Section 3.6) may be further stratified by subject IM status (i.e., subject IM status being positive, negative or unknown) and presented in tables and/or graphically, as deemed appropriate or warranted by the designated study pharmacokineticist, medical monitor, and/or biostatistician. Other stratifications (e.g., based on antibody titer, onset of ADA, etc.) of selected PK, efficacy and safety assessments may also be performed if deemed warranted at the discretion of the pharmacokineticist, medical monitor, and/or biostatistician.